

*GDUFA 2012 REGULATORY SCIENCE INITIATIVES*  
*Part 15 Public Hearing*

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*May 20, 2016*

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*A Matter of Record*  
*(301) 890-4188*

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1 We're going to take the information that we  
 2 learn from this public meeting, in addition to  
 3 submissions to the docket and other sources of  
 4 information, as we develop our 2017 regulatory  
 5 science plan.  
 6 So before we begin, I want to go over a few  
 7 housekeeping announcements. First, please turn off  
 8 any mobile devices as they may interrupt with  
 9 people being able to hear the meeting. We've asked  
 10 that all attendees sign in so we can keep you up to  
 11 date on the research program. The meeting will run  
 12 until approximately 4:30 today.  
 13 We'll be having one 15-minute break in the  
 14 morning and one 15-minute break in the afternoon,  
 15 as well as a lunch session. The restrooms are  
 16 located outside the main entrance to the conference  
 17 room. And there will be a lunch break from  
 18 approximately noon to 1:00 p.m., and there will be  
 19 food and beverages available for purchase in the  
 20 lobby.  
 21 So now I'd like the FDA panel members to  
 22 introduce themselves. And we'll start with my

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1 P R O C E E D I N G S  
 2 (9:00 a.m.)  
 3 DR. LIONBERGER: All right. Good morning,  
 4 everyone. Welcome to both the attendees in the  
 5 conference center and those of you viewing the  
 6 hearing through the live webcast. My name is  
 7 Dr. Robert Lionberger. I am the Director of the  
 8 Office of Research and Standards in the Office of  
 9 Generic Drugs. I'd like to welcome you to this  
 10 Part 15 hearing, Generic Drug User Fee Amendments  
 11 of 2012 Regulatory Science Initiatives: Part 15  
 12 Public Meeting, Request for Comments.  
 13 So I will be the presiding officer today,  
 14 and we have a distinguished panel of experts from  
 15 FDA to listen to the presentations. The purpose of  
 16 the public meeting today is to seek input from a  
 17 variety of stakeholders -- industry, academic,  
 18 patient advocates, professional societies, and any  
 19 other interested stakeholders -- as we fulfill our  
 20 requirements under the GDUFA agreement to develop a  
 21 list of regulatory science initiatives for generic  
 22 drugs.

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1 supervisor, Cook Uhl.  
 2 DR. UHL: Good morning. Cook Uhl, Kathleen  
 3 Uhl, the director of OGD.  
 4 DR. CONNER: I'm Dale Conner, acting  
 5 director, Office of Bioequivalence in the Office of  
 6 Generic Drugs.  
 7 DR. HOLQUIST: Good morning. Carol  
 8 Holquist. I'm the acting deputy director for the  
 9 Office of Regulatory Operations in Office of  
 10 Generic Drugs.  
 11 DR. TOUFANIAN: Good morning. I'm Maryll  
 12 Toufanian, deputy director of the Office of Generic  
 13 Drug Policy.  
 14 DR. BUHSE: Cindy Buhse, director, Office of  
 15 Testing and Research, Office of Pharmaceutical  
 16 Quality.  
 17 DR. BOAM: Good morning. Ashley Boam,  
 18 acting director, Office of Policy for  
 19 Pharmaceutical Quality in the Office of  
 20 Pharmaceutical Quality.  
 21 DR. BARRATT: Ruth Barratt, Office of  
 22 Translational Science at CDER, science advisor.

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

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

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1 The meeting will be transcribed, and copies  
2 of the transcript may be ordered through the docket  
3 or accessed on our website approximately 30 days  
4 after this meeting.  
5 Each speaker will have approximately  
6 10 minutes to present. And after each speaker  
7 presents, five minutes will be allotted to the FDA  
8 panel members to ask questions. So we will ask  
9 questions, really, to try to get people to focus on  
10 what you want us to do and help on the input, is  
11 the main purpose of the questions. So if you, in  
12 your presentation don't tell us what you want FDA  
13 to do, I think you can expect that question from  
14 our panel.  
15 Please remember that the meeting is being  
16 transcribed, so we want all the panelists to use  
17 the microphone when speaking. If we ask you a  
18 question, speakers should also submit their  
19 responses asked by the panel members to the docket.  
20 If a speaker ends early, we'll move on to the next  
21 speaker and leave more time for panel questions.  
22 We'll have a timer light for the speakers to

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

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1 contains confidential information. And this is  
2 detailed in the Federal Register Notice.  
3 Given the agenda, we ask that each speaker  
4 keep to your allotted time so we can keep on  
5 schedule and end on time and meet our breaks and  
6 lunch schedule.  
7 I want to thank everyone for your interest  
8 in the generic drug program and your participation  
9 today. We look forward to a very productive public  
10 hearing. So we'll now begin with the  
11 presentations.  
12 So to start the meeting, I'm going to give  
13 an overview of where we are with the GDUFA  
14 regulatory science. And really, this is looking  
15 back. This is our fourth public meeting, and so  
16 it's really a look-back at the whole aspect of what  
17 we've been doing and what some of the impacts are  
18 to really give a context for the comments now in  
19 terms of that.  
20 So this is part of our GDUFA regulatory  
21 science process where we prepare a yearly list of  
22 research priorities with input from all

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1 stakeholders. The results of last year's input,  
2 our FY 2016 priorities, were post-market evaluation  
3 of generic drugs, equivalence of complex products,  
4 equivalence of locally-acting products, therapeutic  
5 equivalence evaluation and standards, and  
6 computational and analytical tools -- a strong  
7 scientific foundation for the generic drug program.  
8 As we've been implementing this, we  
9 implemented this mainly through both internal and  
10 external research collaborations. We have  
11 approximately a hundred ongoing research  
12 collaborations that come out of these regulatory  
13 science inputs. So we're partnering with  
14 scientists around the world, leading experts,  
15 engaging them to build a strong scientific  
16 foundation for the generic drug program.  
17 Under GDUFA, this has really allowed us to  
18 scale up the scientific foundations to  
19 approximately 10 times the size of the pre-GDUFA  
20 effort that FDA was able to make in generic drug  
21 regulatory science. In addition to external  
22 collaboration, it supports work in our FDA labs; it

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1 supports post-doctoral fellows, both in our offices  
2 and our laboratories, who do a lot of the internal  
3 activities.  
4 Linked into this, the office I lead in OGD,  
5 the Office of Research and Standards, we manage  
6 most of these research activities and we really try  
7 to link them in to the development of our guidances  
8 and our responses to questions that industry asks  
9 through the controlled correspondence process to  
10 pre-NDA meetings.  
11 So the results of the regulatory science  
12 research feed into the standards for generic drug  
13 approval and evaluation that FDA uses. So we try  
14 to have a very strong link with that, and I'll try  
15 to point out that as we go through the program.  
16 To give a sense of how much we've increased  
17 because of the GDUFA resources that have been  
18 supplied to regulatory science here, from looking  
19 back to the three years prior to GDUFA, you can see  
20 there's about a tenfold increase in the regulatory  
21 science activity that OGD has been conducting  
22 because of GDUFA. And this leads to -- as we begin

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1 these projects, each year we award new projects.  
2 Many of them are multi-year projects, so there's a  
3 large number of projects that are under management.  
4 So we've been continually growing the program.  
5 Now, by the fourth year of the program,  
6 we're reaching approximately a stable plateau of  
7 activity. But there's been a huge scale-up in  
8 activity, a large number of resources. But I want  
9 to talk today about some of the impacts that come  
10 out of this research activity.  
11 As we do that, and I'll come back to these  
12 at the end when we're looking for comments, the  
13 areas of impact of our regulatory science program  
14 are generic access in all product categories. This  
15 is a strong focus. It's critically important to  
16 both the industry and the American public that  
17 generic products be available wherever possible.  
18 As we go through today, you'll see that even  
19 given the great success of the generic drug  
20 program, reaching I think it's 88 percent of the  
21 prescriptions dispensed being generic products,  
22 still in that remaining 12 percent there are a

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1 large number of very complex products without  
2 generic drug competition. And that's a big focus  
3 of the access aspect of our regulatory science  
4 program. And if you think about the return on  
5 investment of that, each one of those complex  
6 products is probably a billion-dollar market.  
7 So everything I'm going to be talking about  
8 in terms of complex product access, each one of  
9 those represents probably at least a billion  
10 dollars in savings to the American public a year if  
11 generic products are available in that category.  
12 So that's the scale of impact that we're talking  
13 about.  
14 If it's not a billion dollar-impact, it  
15 probably doesn't make it even into this  
16 presentation. So there's still very significant  
17 areas where the scientific challenges prevent  
18 access to generic products, and we're working very  
19 diligently and collaboratively to address those.  
20 The second area of impact is in confidence  
21 in generic drug substitution. As we've moved from  
22 an environment when I first joined FDA in 2003,

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1 about 50 percent of the prescriptions dispensed  
2 were for generic drugs, to where we're nearing 90  
3 percent.  
4 So that's a much bigger responsibility for  
5 both FDA's generic drug program and the industry  
6 that's providing that. You're providing the drugs  
7 that almost everyone is taking for almost every  
8 condition that they're being treated for.  
9 So it's important that there be strong  
10 confidence in the products that we're producing,  
11 the regulations that are governing them, that  
12 people know that they'll be substitutable. And  
13 that's what the industry intends. That's what FDA  
14 believes when we approve your products.  
15 So there's a strong research focus on  
16 identifying areas and research that can sustain  
17 that confidence. If you don't have confidence,  
18 it's a very unstable situation, given the great  
19 responsibility for that large part of the  
20 pharmaceutical products that the American public  
21 uses.  
22 The third impact is really developing the

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1 tools for both product development and product  
2 review. So these could be computational, modeling  
3 tools. Yesterday we had a day-long workshop on  
4 oral absorption modeling. Still, solid oral dosage  
5 forms are the vast majority of generic drugs. So  
6 tools that predict what happens in your  
7 bioequivalence studies that aid your formulation  
8 design are essential to the efficient development  
9 of generic drugs and the review of those products.  
10 But these tools also touch more complex  
11 products and analytical and computational methods  
12 across the scope. And this is an area where  
13 there's huge benefit to industry in using the best  
14 available tools, and as I said, by engaging with  
15 leading pharmaceutical scientists who bring that  
16 information into our review processes.  
17 So when we meet with you on a pre-NDA  
18 meeting on a complex product, we've also been  
19 engaging with experts in that area as well. So  
20 we're able to really be on the leading edge of  
21 science as we do that, and I'll talk about some  
22 examples where that's led to recent approvals of

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1 generic products.  
2 So as I said, the success of generics is a  
3 large fraction of dispensed prescriptions and the  
4 limited cost, but there's still a lot of things on  
5 the table.  
6 As we move toward translating the regulatory  
7 science results into generic drug applications and  
8 approvals, one way we do this is through the  
9 bioequivalence guidances and the product-specific  
10 information. And you can see that the number of  
11 guidances is growing each year under GDUFA. We're  
12 maintaining this, and we project that this year  
13 we'll produce even more than the year before.  
14 But one thing that you don't see in just  
15 looking at the numbers is that the fraction of  
16 these guidances that are for complex products is  
17 increasing. So we have about 1500 guidances  
18 currently posted. The initial surge of that was  
19 capturing a lot of the immediate-release products.  
20 Now, as we're moving forward, a lot of the  
21 work that's going on in these guidances is much  
22 closer linked into the regulatory science

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1 activities where we need research in order to  
2 develop guidance on the more complex products. So  
3 this is a significant way that you see outcomes  
4 from the regulatory science program.  
5 Just to give a sense of what I'm going to  
6 talk about, generic access in all the product  
7 categories -- we've tried to develop a research  
8 portfolio that's broad across a range of  
9 activities. So I'll talk today about complex  
10 active ingredients, topical dermatological  
11 products, inhalation products, ophthalmic products,  
12 nasal products, liposomes and nanomaterials,  
13 microsphere products.  
14 As I mentioned, each of these is probably at  
15 least multi-billion dollar market of products  
16 without generic competition available because of  
17 some of these scientific challenges.  
18 For the second topic on the confidence in  
19 generic drug substitution, I'll talk about our  
20 brand-to-generic switching studies in patients,  
21 which we have begun to present at scientific  
22 meetings, and really changing some of the debate

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1 about generic substitution; talk a little bit about  
2 post-market surveillance of generic substitution,  
3 and our product-specific standards.  
4 In the tools for development and review,  
5 we'll talk about some of our modeling and  
6 simulation activities, but also the analytical and  
7 in vitro tools that help really develop more  
8 complex products. If you have an in vitro release  
9 test, that's something you can use to guide your  
10 development of a bioequivalent product, and many of  
11 our research projects are touching on that critical  
12 aspect of pharmaceutical development.  
13 We have approximately 20 collaborations with  
14 different FDA labs on new analytical methods that  
15 impact some of our generic drug approvals. I'll  
16 talk a little bit more in specific examples as we  
17 move forward.  
18 So focusing on the little bit deeper  
19 analysis, going through some of these product  
20 categories under generic access, one area of  
21 complex products are the complex active  
22 ingredients: peptides, complex mixtures, natural

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1 source products.  
2 Under GDUFA, we've approved the first ANDA  
3 for glatiramer acetate generic. This is an  
4 immensely complex product. It wouldn't have been  
5 possible without significant scientific work from  
6 our scientists and our FDA lab collaborators to use  
7 high-resolution analytical methods to support the  
8 evaluation of those ANDAs. It's a critical  
9 approval, a multi-billion dollar drug product, many  
10 long, complex review processes. Without a strong  
11 scientific foundation, you'll never be able to  
12 approve products like that.  
13 To move forward in other longstanding  
14 complex products, we have draft guidances under  
15 GDUFA for conjugated estrogens, a natural-source  
16 product that's challenged FDA for 20 years. And we  
17 have a guidance with extremely detailed information  
18 about analytical methods, developed in conjunction  
19 with our FDA laboratories in St. Louis, to provide  
20 a clear pathway for how to analyze these types of  
21 products. There's still a lot of work to do for  
22 the applicants to match up these complex products,

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1 but we've really provided, I think, a clear pathway  
2 for that in these guidances.  
3 We have other draft guidances on other  
4 complex mixtures as well, so the sevelamer  
5 products, talking about characterization, natural  
6 source mixtures for the omega-3 products.  
7 On our guidance agenda, we have on our  
8 public guidance agenda a guidance on rDNA origin  
9 reference products and the pathway for generic  
10 versions of those that we hope will be appearing  
11 sooner this year. But it's on our public agenda.  
12 We've been able to clear the backlog on  
13 controlled correspondence questions related to this  
14 type of peptide sources. This is another complex  
15 category where access to generics was blocked in  
16 the past, but through the scientific efforts that  
17 we've made, we've been able to open up that pathway  
18 moving forward.  
19 We still have research activities in this  
20 area. Many of these complex products raise issues  
21 related to impurities and immunogenicity. And  
22 we're working with many FDA internal collaborators



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1 to develop better tools for assessing that, for  
2 identifying if there are differences in impurities,  
3 whether they'll cause any risk or not.  
4 We continue to work on the high-resolution  
5 analytics and multivariate data analysis with our  
6 FDA lab collaborators to develop the analytical  
7 tools that will help advance this area. But you  
8 can see here the huge impacts of a strong  
9 scientific foundation on pathways towards complex  
10 generics, and even approvals of very complex  
11 products.  
12 The challenge here -- just this cartoon is,  
13 what you try to do in these analytical methods is  
14 you look at some of the pieces from your analytical  
15 methods, and through the combination of complex  
16 modeling and simulation approaches and the  
17 analytical methods, try to reconstruct similarity  
18 of the products. So there's a lot of complex  
19 science that goes on behind these approvals, and  
20 the resources from the GDUFA program really support  
21 that activity.  
22 Probably the largest category where there's

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1 no generic competition are the inhalation products.  
2 And we have significant research activity here  
3 looking at the role of dissolution, particle size,  
4 PK studies. We have CFD modeling projects.  
5 We have research that's supporting looking  
6 for areas where we can move away from having a  
7 requirement of being Q1/Q2 for the inhalation  
8 products to understand. For excipients that have  
9 been used in other inhalation products, they may be  
10 acceptable under certain conditions in identifying  
11 the analytical and in vivo studies that are needed  
12 to support that.  
13 So there's constant research to advance our  
14 understanding of this product category, but we've  
15 been extremely successful in GDUFA at translating  
16 these research findings into guidances in this  
17 particular category.  
18 So as of our April posting, we now have  
19 13 product-specific guidances for inhalation  
20 products available. So when we started GDUFA we  
21 had none, no pathway for this I think multi-tens of  
22 billions of dollar a year market. No guidances at

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1 all. Right now we have 13 available for different  
2 product categories. So there's significant  
3 scientific activities that support this.  
4 We recognize that these products and  
5 these -- what we're asking in the guidance is very  
6 challenging in some places, so we still have  
7 research activities to improve, identify better  
8 dissolution methods for inhalation products that  
9 may help you select particle -- raw material  
10 suppliers.  
11 It may help us review that to look at  
12 alternatives to some of the very challenging  
13 studies that some of these guidances ask for. But  
14 we've made a huge effort in providing guidance  
15 across this very large and important product  
16 category.  
17 Really, this pushes a lot of the  
18 responsibility onto the industry to engage with  
19 these guidances to develop products; if you have  
20 questions, to meet with us around this area. We've  
21 also had significant pre-ANDA meetings with  
22 companies working in this space, responding to

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1 these guidances, and we've prioritized those  
2 because this is a complex product category with  
3 essentially no generic competition.  
4 In ophthalmic products, again, there's been  
5 very challenging generic products that require very  
6 difficult clinical endpoint studies in the past to  
7 develop. We've been developing guidances with  
8 alternatives to those, two guidances specifically  
9 under GDUFA for some of the ophthalmic emulsions  
10 that provide what we call a Q3 approach.  
11 So this is having a formulation that has the  
12 same active and inactive ingredients, but also the  
13 same microstructure as well, as we've determined  
14 for these cases that that's the most appropriate  
15 bioequivalence method. It's much more sensitive  
16 and reproducible than a potential clinical endpoint  
17 bioequivalent study for those products.  
18 We have a broad portfolio of research  
19 activities in the ophthalmic product space that  
20 includes modeling and simulation, but also  
21 significant efforts on in vitro release methods for  
22 ophthalmic suspensions, ophthalmic emulsions,

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1 ophthalmic ointments, to really broaden the ability  
2 to apply these Q3 approaches to other dosage forms  
3 as well. We've also done a significant amount of  
4 guidance development in this ophthalmic space.  
5 We've produced 10 guidances for ophthalmic  
6 suspensions.  
7 We're engaged in research activity to  
8 improve ways to do some of the very difficult and  
9 challenging aqueous humor PK studies, and also the  
10 significant focus of research on the Q3  
11 opportunities in this case, again, another large  
12 product category with very limited competition for  
13 the ophthalmic suspensions, ointments, and emulsion  
14 where there's been significant research activity,  
15 very significant guidances coming out that will  
16 enable competition in this area in the future.  
17 In the nasal product category, we have  
18 research activities looking at the role of PK  
19 studies, in vitro and in vivo modeling projects.  
20 But I want to point out also one innovative  
21 technology, the MDRS particle sizing. This is  
22 Morphology-Directed Raman Spectroscopy. This is an

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1 instrument that wasn't even available until 2012,  
2 but it was used to support an ANDA approval in  
3 2016.  
4 So before this technology has even been used  
5 in a new drug application, they used it to support  
6 a generic drug application. And this essentially  
7 allows you to, if you have a suspension that has  
8 two different types of particular sizes, do a  
9 particle size comparison of only the API active  
10 ingredient. So this is critical for doing a Q3  
11 analysis of some of the more complicated  
12 suspensions.  
13 We wouldn't have been able to do this. We  
14 wouldn't have been able to approve this product,  
15 unless we had one of these pieces of equipment in  
16 our FDA lab to understand how it works to be able  
17 to give good responses to the submission to analyze  
18 them correctly. So without our investment in the  
19 regulatory science foundation, we wouldn't be able  
20 to approve these complex products through this type  
21 of pathway and using this type of very current new  
22 scientific technologies to support approvals of

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1 these complex products. And this is a  
2 category -- there weren't any generics in this  
3 space before this approval. It was supported by  
4 this novel technology.  
5 Another product category where there's  
6 significant lack of generic competition is in the  
7 topical dermatological products. This is a little  
8 bit different. There, we have longstanding  
9 clinical endpoint studies in this area that have  
10 been used. So there are some generic products  
11 available. But if you look at the category -- and  
12 we have for the topical corticosteroids a  
13 pharmacodynamic endpoint approach available.  
14 But compared to the broader population of  
15 products, there's still a large number of topical  
16 products that lack generic competition in this  
17 area. But it's a much broader number of products  
18 than a lot of the other complex products.  
19 But we have a very significant coordinated  
20 research activity to advance the Q3 equivalence  
21 approaches for these products. We're collaborating  
22 with people round the world. In this project,

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1 we're working with people in Europe, Australia, and  
2 the US, generating new in vivo data. We're  
3 manufacturing semisolid formulations,  
4 characterizing them. We have modeling approaches  
5 integrated into this approach.  
6 We've made significant progress in this  
7 area. We've done, as an example, some Q3 testing  
8 on some acyclovir creams. We've obtained  
9 formulations from around the world to look at them,  
10 characterize them through all of the different  
11 characterization methods are available through the  
12 rheology, the particle size characterization.  
13 We've looked at them in in vitro permeation  
14 tests, which are excised human skin studies. We've  
15 looked at them through in vitro release tests,  
16 which are artificial membranes, putting together a  
17 full picture to understand which of these tests are  
18 appropriate for comparing formulation differences.  
19 I think one of the things I'm most impressed  
20 with for the regulatory science program in the  
21 topical area is an in vivo study that we've done on  
22 what's called open flow microperfusions. This is a

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1 type of microdialysis. And we did a 20-person  
2 study looking at two different -- comparing the US  
3 reference product to a product that's available in  
4 Europe.  
5 This study shows -- one of the challenges  
6 with the microdialysis studies in the past has  
7 been, are they reproducible? So this is a  
8 replicate design study. We show that using the  
9 reference product, you get very reproducible  
10 results.  
11 Our investigator in this did something very  
12 novel. So essentially, all of the microdialysis in  
13 the skin data that's available in the past has been  
14 limited to about 6 hours because you had to hook  
15 people up to these giant pumps. They couldn't  
16 move, so they were stuck there.  
17 New technology. These are wearable  
18 microdialysis devices. So people look like cyborgs  
19 in the pictures with them, but they can walk  
20 around. You can then get out to 40 hours of data,  
21 looking at the long time, so just basically the  
22 leading edge of approaches to this type of new in

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1 vivo study that is directly relevant to drug  
2 delivery across the skin, again, funded by -- and  
3 publication in this is under preparation. Should  
4 be available soon. We've talked about these  
5 results at public meetings as well.  
6 We've shown that in a reasonably-sized  
7 study, 20 subjects, you can demonstrate  
8 bioequivalence between the replicate studies, and  
9 you can also show that a formulation that we know  
10 is Q3 different also has different drug delivery  
11 and doesn't show equivalence as well; so a strong  
12 development of a potential new in vivo approach to  
13 this as well as new characterization- based  
14 approaches.  
15 We've also done work on looking at the IVPT  
16 and developing ways to do bioequivalence  
17 comparisons for these types of in vitro permeation  
18 tests as well that could be used for  
19 bioequivalence. But also, these studies are used  
20 right now in product development to select  
21 formulations and really help understand a lot  
22 of -- they're also used for post-approval changes

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1 as well, so having better ways to do statistical  
2 comparisons for them.  
3 By lining these up with different  
4 formulations, we've been able to compare between  
5 different labs, different collaborators in  
6 different labs, to help us develop better protocols  
7 for how to do these in vitro permeation tests.  
8 Another complex product category is the  
9 liposomes and nanomaterials -- seven grants on in  
10 vitro release, product characterization,  
11 identifying the critical manufacturing variables.  
12 We have guidances now on many different liposomal  
13 products under GDUFA guidance, on some of the  
14 nano-sized iron chelate products as well, to help  
15 develop generic versions in this complex product  
16 category.  
17 We have a significant program in looking at  
18 some of the long-acting injectables and microsphere  
19 controlled-release products, nine grants looking at  
20 different aspects of these products. We've  
21 developed guidance on some of these products under  
22 GDUFA. I have some pictures here of some of the

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1 microspheres that we're doing.  
2 Here we've also seen a significant interest  
3 in the number of pre-ANDA meetings. There seems to  
4 be a large interest in these product categories.  
5 They're very long-acting, so there could be  
6 challenges to do PK studies for long periods of  
7 time. So we're really focused on also the  
8 characterization of these materials as well.  
9 So this is a significant area of very  
10 limited generic competition in this product  
11 category that we think that will be enabled, and  
12 will have a much stronger fundamental of the  
13 material science that drives drug release in these  
14 products from these research activities. And this  
15 will feed into our discussions with you in pre-ANDA  
16 meetings, our views of these products, and our  
17 development of guidances in this product category.  
18 In looking at complex drug-device  
19 combinations, this includes the dry powder inhaler,  
20 the metered dose inhalers I mentioned earlier,  
21 nasal sprays, but also transdermal systems, auto-  
22 injectors. This is an important area for research

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1 to understand the patient factors that affect how  
2 people use devices.  
3 This is something that's an emerging area  
4 for the review of these products and developing  
5 these products. How do you compare the devices?  
6 How similar do they have to be to be a  
7 substitutable generic product? What types of  
8 studies and comparisons of the device you have to  
9 use?  
10 So a lot of our thinking of this is fed into  
11 our guidances on the metered dose and dry powder,  
12 especially the dry powder inhalers, where there's  
13 lots of diversity in the devices.  
14 But also on our guidance agenda that will  
15 appear soon, there's a new guidance on adhesion for  
16 transdermal systems that's been developed as well  
17 that will be a transformation on how we do the  
18 adhesion bioequivalence studies. We have research  
19 activities looking at the irritation type studies  
20 for transdermal systems as well, as well as the  
21 patient use factors.  
22 So again, significant efforts in trying to

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1 understand the regulatory review issues related to  
2 these more complex drug-device combination products  
3 that are eligible for generics can reference these  
4 products.  
5 Another significant guidance that was  
6 developed is our guidance on generic abuse-  
7 deterrent formulations. This guidance, that was  
8 released in March as a draft, provides a path for  
9 generic versions of abuse-deterrent opioid  
10 formulations; relies primarily on a comparative in  
11 vitro and occasional PK studies. But the GDUFA  
12 research support was essential to this guidance, so  
13 this has a huge public health impact. It's a very  
14 controversial area. We have to have very strong  
15 scientific foundations for anything we do in this  
16 area.  
17 We had a contract with NIPTE through our  
18 GDUFA regulatory science research to do external  
19 research on this, but also significant support for  
20 ORISE fellows in FDA's labs for testing these  
21 products. So without this recent GDUFA research,  
22 we wouldn't have that guidance. We wouldn't have

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1 that impact. We wouldn't have a pathway for  
2 generic versions of currently approved abuse-  
3 deterrent formulations.  
4 I think this will be also an important part  
5 of FDA's overall view of the landscape of abuse-  
6 deterrent formulations. Once you have a pathway  
7 for generic versions, that gives people confidence  
8 that as products move towards abuse-deterrent  
9 formulations, there will be generic versions  
10 available in the future now that we have this  
11 guidance and a clear pathway for that. But without  
12 GDUFA regulatory science support, I don't think  
13 we'd be anywhere near this point without the data  
14 that we developed, both internally and externally,  
15 on this very complex issue.  
16 Now, changing a little bit to talk about the  
17 confidence in generic drug substitution. So one of  
18 the things we've been doing in this area is  
19 brand-to-generic switching studies in patients. As  
20 many of you know, almost all generic products are  
21 approved based on studies in healthy subjects  
22 because we think that that's really the best test

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1 of the formulation comparison. So from a  
2 scientific point of view, we have strong reasons to  
3 understand that.  
4 But sometimes, if you think from a clinical  
5 perspective, you say, well, these products are used  
6 by patients, and you're testing them in healthy  
7 subjects. Does that make sense? So we've worked  
8 in several areas where there's been significant  
9 questions about generic substitutions,  
10 specifically, first, for anti-epileptic drugs and  
11 immunosuppressant drugs, to do studies that look at  
12 generic substitution in patients.  
13 Essentially, from FDA's point of view, we  
14 absolutely believe that these studies are going to  
15 show they're equivalent. We've really focused on  
16 what we think is the strongest, most sensitive test  
17 of the formulation. But this really helps the  
18 broader community understand generic drug  
19 substitutability.  
20 So we've conducted these studies. We give  
21 an overview of what they look like. These are  
22 generally replicate studies where people go from

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1 the generic to the brand to the generic to the  
2 brand, back and forth. We generally look at PK  
3 outcomes, but we show very clearly -- this is the  
4 first study that was conducted at the University of  
5 Maryland with Jim Polli, who I think will be  
6 speaking later today, bioequivalence in generic and  
7 brand product, PK profiles essentially  
8 superimposable between the brand and generic.  
9 We did a similar study with a different  
10 group, looking at generic-to-generic substitution;  
11 again, similar type of design, here looking at what  
12 they thought was the lowest generic versus the  
13 highest generic, trying to look at the extremes of  
14 the space, to get approved under our  
15 standards -- again, completely bioequivalent in  
16 patients in both of these cases. A similar type of  
17 study design in transplant patients on generic  
18 versions of tacrolimus; again, direct comparison in  
19 patient population bioequivalence as well.  
20 So we've begun to publish these results. As  
21 we've published these papers, there's been  
22 accompanying comments or editorials about this.

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1 And I think this really shows the significance that  
2 this type of data can have on the community  
3 perception of these drugs.  
4 Organizations that have been generally  
5 skeptical of generic substitution said these  
6 studies really are a step forward in addressing  
7 their concerns. We worked very closely with these  
8 communities to say, what kind of studies would  
9 address your concerns about generic substitution?  
10 As we follow that up with the publication  
11 from the second study, again people have questioned  
12 the safety of generic substitution. Quite  
13 reassuring that organizations with a negative  
14 attitude to substitutions would consider reviewing  
15 their position. So I think these new sets of data  
16 are an important and critical part of understanding  
17 confidence in generic drug substitution.  
18 It's a very different way to approach  
19 questions about generic substitutability, but it  
20 really -- these are the most expensive type of  
21 studies that we support under our GDUFA regulatory  
22 science program. So it requires significant

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1 resources to do these types of studies, and conduct  
2 them, and make them publicly available from that.  
3 In this area we're also looking at -- the  
4 question is about substitutability, confidence in  
5 generic substitution. So we've also funded  
6 research to help us get an idea about what are the  
7 patient perceptions about generic drugs? What are  
8 physician perceptions about that? So we've  
9 published some of this work as well to understand  
10 what drives questions about generic  
11 substitutability, both in patients who generally  
12 prefer generic products and also physicians  
13 confidence in this.  
14 But again, I think we've seen that -- our  
15 collaborators on this saw an increase in confidence  
16 in generic drug substitution over the last few  
17 years. And I think it's very useful to see that,  
18 but this is a way to measure broadly how we're  
19 doing as an industry and a generic drug program in  
20 reaching out to both patients and physicians about  
21 generic drug substitutability. So this has been  
22 part of our generic drug research program, to

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1 provide this baseline information, as well.  
2 Other aspects of confidence in generic  
3 substitution have to do with making sure that we  
4 are monitoring the products that we approve  
5 effectively. And there's really two large sets of  
6 data that you could potentially look at to say, are  
7 generic products being substituted effectively?  
8 So we look at adverse event reports. These  
9 have very significant challenges for using them to  
10 look at generic drug substitution. Oftentimes  
11 people don't know which generic product they're  
12 taking. There's huge potential reporting biases.  
13 I've been switched to a generic. Am I more likely  
14 to complain about something that just was a normal  
15 expected adverse event from the brand product?  
16 Questions about normalization.  
17 We have some research activities looking at  
18 authorized generics. So these are generic products  
19 that are essentially the exact product as the brand  
20 product, just marketed differently, to see what  
21 types of adverse events people report about those  
22 products. We do actually see complaints about

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1 generic substitution with authorized generics. So  
2 that's an interesting, unique, natural experiment  
3 to help understand some of the biases in figuring  
4 out what's really significant.  
5 The other big chunk of data that you could  
6 look at are either electronic healthcare records or  
7 insurance claim data. These have some advantages.  
8 They oftentimes can be linked into an NDC code to a  
9 specific product. But you may see substitution  
10 events here.  
11 But there are significant challenges with  
12 how to look at this data to understand questions  
13 about generic drug substitution. So we have some  
14 research activities to look at substitution  
15 patterns -- what do you expect to see? What would  
16 be unusual? Looking at how to compare other  
17 things.  
18 But I think in the future, these datasets  
19 are going to become more -- we're moving toward a  
20 big data future. So these datasets are going to be  
21 available to more and more researchers, more and  
22 more generic companies. So we have to be prepared

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1 to think about how we're going to analyze generic  
2 substitution questions in these types of  
3 information sets and do it in a way that gives us  
4 good information.  
5 I think there's lots of ways in these  
6 retrospective datasets to do bad studies, and that  
7 can give misleading results about generic products.  
8 So it's really important that we have a broad-based  
9 research program in understanding how to do these  
10 types of analysis well for these specific questions  
11 about generic drug substitution.  
12 The other side of confidence in generic drug  
13 substitution is making sure that people have  
14 confidence in the standards that we as FDA are  
15 applying to products. And two areas that we  
16 focused research efforts on are for narrow  
17 therapeutic index drugs.  
18 So we're really moved significantly, under  
19 the first few years of GDUFA, to providing  
20 guidances identifying which products we think have  
21 a narrow therapeutic index, and having tighter  
22 bioequivalence standards on that.

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1 We think that sort of risk-based standard,  
2 the idea that there's higher- and lower- risk drugs  
3 and they should have tighter standards for the  
4 higher-risk products, I think is a strong part of  
5 confidence. I think there's been -- there's some  
6 challenges as we change guidances and evolve our  
7 standards in this area. But this is moving toward,  
8 I think, a much stronger foundation for our  
9 program. As we get ahead in guidance development,  
10 we should be making these decisions on which drug  
11 we think have a narrow therapeutic index very soon  
12 after the new drug approval.  
13 We have a new internal working group to  
14 coordinate activities between OGD, OCP, OND around  
15 which drugs have a narrow therapeutic index. So  
16 what you can expect to see in the future is these  
17 decisions made much earlier, before any kind of  
18 generic drug development happens.  
19 Similar thing with a partial AUC. This is  
20 an approach to say, there's a smaller number of  
21 products that may have very critical -- the PK  
22 profiles being much more similar than needed. And

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1 we work closely to develop those cases. And again,  
2 as we move our guidance development closer to the  
3 new drug approval, we want to have these questions  
4 identified early.  
5 So this links into the tools for  
6 development. Both of these examples -- narrow  
7 therapeutic index drugs, partial AUC  
8 comparisons -- really are driven by what I call the  
9 pharmacometrics for generics. This is the PK/PD  
10 response.  
11 Which drugs have a sharp exposure-response  
12 relationship? Which drugs have a close connection  
13 between the shape of the PK profile and their  
14 pharmacodynamic responses? This is a scientific  
15 question that's going to determine whether we have  
16 tighter standards for these two categories.  
17 So we're trying to support strong program  
18 internally and through research in what I call the  
19 pharmacometrics for generic drugs. This is the  
20 PK/PD modeling that can support these risk-based  
21 decisions, provide the input into this. And these  
22 two critical questions are the most important

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

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

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

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

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1 GI tract?

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

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

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

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

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

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

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

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

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

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

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1 development? So we want to develop our future  
2 agenda in these types of categories. So I'll try  
3 to fit our questions and inputs into your  
4 discussion as we have the discussion going forward.  
5 But just to conclude my initial discussion,  
6 there's a huge public health impact for a  
7 relatively small regulatory science investment.  
8 All right? My return on investment calculation  
9 says that if we approve generics in even one of  
10 these categories, that's a multi-billion dollar a  
11 year benefit for a program whose net cost over five  
12 years is around \$100 million. So just one of these  
13 product categories can give you 100-fold return on  
14 investment. And there's multiple multi-billion  
15 dollar categories that are being addressed by this.  
16 This broadly puts a strong scientific  
17 foundation for our program; that's of huge benefit  
18 to the industry and to the public. We've taken  
19 these research activities. We're driving guidance  
20 development for complex products. The inhalation  
21 guidance, I think, is the leading edge. That's the  
22 one we've recognized for a long time is the most

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1 significant one.  
2 You see there, as these research projects  
3 drive in, you see this surge of guidances across  
4 that product category, 13 in that specific category  
5 alone, enabling broad generic competition in a very  
6 complex product space.  
7 A lot of these issues are very complicated,  
8 not just externally but also internally. We have  
9 to get alignment across -- in order to have a  
10 guidance on abuse-deterrent formulations or  
11 adhesion or rDNA source RLDs for peptides, there's  
12 a huge number of internal stakeholders have to get  
13 aligned on that.  
14 The FDA research activities in there can be  
15 very critical in driving that. They provide data  
16 that people can look at and say, well -- people can  
17 raise hypothetical concerns. We have real data to  
18 address that. We can help drive the alignment on  
19 getting a policy or guidance implementation of  
20 these complex issues out. So there's lots of  
21 things going on behind the scenes on many of these  
22 complex issues that are in addition to the publicly

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1 available science.  
2 The confidence. I think the FDA scientific  
3 support for confidence in generic substitution is  
4 very unique. Even if a generic company went out  
5 and did these studies on generic substitution,  
6 right, they'll say, well, you have an interest and  
7 a bias in that.  
8 I think when FDA supports them, when we  
9 partner with academic groups that are  
10 essentially -- and some, in some cases, have been  
11 skeptical of generic substitution in the past. I  
12 think that makes a much, much stronger public  
13 statement of confidence in generic products that  
14 really has the biggest possibility for impact on  
15 perhaps even changing some of these groups that  
16 say, don't substitute approved generic products.  
17 I think, from FDA's point of view, we  
18 wouldn't approve the products if we didn't think  
19 they were substitutable. And we hope that people  
20 will begin to understand that and see that  
21 perspective. But this type of data really provides  
22 very strong prospective studies designed to answer

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1 those questions and prove that.  
2 The tools that we're developing -- the goal  
3 is faster development and review. If you have  
4 right modeling and simulation tools to predict  
5 what's going to happen in the bioequivalence study,  
6 if you have the right in vitro characterizations to  
7 say, what's the critical attribute of the brand  
8 product and does my product match that, that's  
9 going to drive faster product development.  
10 But that's also going to drive a faster  
11 review. If you have strong tools that say, this is  
12 the right study, this is the right analytical data,  
13 we'll be able to make better decisions and  
14 evaluations about that. And by having these tools  
15 publicly available, everybody knows what they are.  
16 They become commonly established. That feeds into  
17 this cycle.  
18 I think, from my perspective, it's been  
19 incredibly exciting to be involved in the growth of  
20 this part of the generic drug program. And the  
21 input that we get from these public meetings and  
22 the comments to the docket really help align what



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1 we're doing with what the needs of the industry and  
2 the public are.  
3 I really personally appreciate all of the  
4 comments that you've given. And I think it's just  
5 incredibly exciting to be involved in all of these  
6 different research activities across FDA with all  
7 of our external collaborators.  
8 So with that, we will be moving on to our  
9 first speaker of the day, and I have to go back to  
10 my seat so I can change roles. So our first  
11 speaker will be Dr. Michael Fischer from Brigham  
12 and Women's Hospital, Harvard Medical School, to  
13 talk about regulatory science for generic drugs.  
14 So welcome.  
15 Presentation – Michael Fischer  
16 DR. FISCHER: Great. Thank you very much.  
17 Thanks for the introduction and for the opportunity  
18 to speak here. As Dr. Lionberger said, my name is  
19 Mike Fischer. I'm a primary care physician and a  
20 researcher in the Division of Pharmacoepidemiology  
21 and Pharmacoeconomics at Brigham and Women's  
22 Hospital, affiliated with Harvard med school. I'm

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1 presenting on behalf of a group of several of us in  
2 our division who do work in this area.  
3 Dr. Lionberger was kind enough to cite a  
4 couple of the projects we have ongoing, and it's a  
5 nice chance to thank the office for the chance to  
6 collaborate on that initial work. And what I'll be  
7 doing is making some suggestions on what those of  
8 us in our group working on this see as exciting new  
9 areas to move into in the coming months, years, and  
10 into the future.  
11 Since it's in the printed materials, I won't  
12 read what's on this disclosure slide in terms of  
13 potential conflicts of interest. It's all there  
14 printed for those as needed.  
15 Quick orientation on what our division is.  
16 The Division of Pharmacoepidemiology and  
17 Pharmacoeconomics, besides having large business  
18 cards -- although I think the FDA has equivalently  
19 long titles for their offices, so I feel much more  
20 at home here -- we're a group of 18 faculty  
21 members. We mix health services research, drug  
22 safety and outcomes research, a lot of methods

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1 work, law and policy.  
2 We have a diverse portfolio of funding -- as  
3 I mentioned and as Dr. Lionberger cited, some work  
4 with the FDA, but also grants from many federal and  
5 federally affiliated agencies, as well as a variety  
6 of collaborations with manufacturers, with  
7 insurers, and with others.  
8 We have several specific programs. I direct  
9 the National Resource Center for Academic  
10 Detailing, which is supported by AHRQ and does  
11 direct outreach to front line clinicians. Aaron  
12 Kesselheim, who testified at this meeting last  
13 year, runs something called PORTAL, the Program on  
14 Regulation, Therapeutics and the Law, that looks at  
15 regulatory science. Our colleague, Niteesh  
16 Choudhry, runs the Center for Healthcare Delivery  
17 Sciences. And then we have other core faculty who  
18 have various roles at PCORI, FDA, Sentinel, and  
19 others.  
20 So that's who we are. Let me transition now  
21 to what we want to put forward as suggestions. And  
22 the format for the several slides I'll have, just

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1 since we used the same format for all of them, is  
2 basically we'll cite a piece of existing evidence  
3 to set the stage. I'll be hitting those very  
4 briefly, just given the time constraints that we  
5 have.  
6 Then a couple -- one or two research  
7 questions that we would suggest for the coming  
8 months and years. And then a quick note about why  
9 we think that's relevant for this office, what the  
10 results of that sort of research might offer as  
11 useful information.  
12 So the first area are single- or limited-  
13 source generic products. This is a paper that's  
14 currently under review out of our group. But over  
15 a third of the entities eligible for generic  
16 competition have three or fewer approved generics.  
17 And as I think lots of people in this room would  
18 know, many are single source.  
19 So from a research point of view, trying to  
20 get a better understanding of the predictors of  
21 when a generic agent will become available only  
22 from a single source would be a productive area for

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1 study.

2 From a regulatory point of view, being able

3 to identify proactively, prospectively, when that

4 situation may arise and sort out what might be

5 appropriate targets, either for regulatory or

6 incentive-based approaches when these situations

7 are coming up, might help address that problem.

8 Similarly, thinking about the next stage in

9 that cascade, how does a single-source generic

10 change utilization patterns or clinical outcomes

11 when compared to multi-source generic medications?

12 Understanding the impacts of, especially

13 single-source generics, again would provide useful

14 information for FDA regarding the impact of

15 policies that might be considered, or eventually

16 implemented, to address the challenge of single-

17 source generics.

18 The next topic we wanted to put forward for

19 consideration is generic medication shortages.

20 There, I think again, the background would be

21 familiar to most of the people listening to this

22 session. Over the last six years, over a thousand

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1 drug shortages were reported to the FDA. So there

2 are several research questions that we thought

3 would be of interest in this area.

4 When these generic drug shortages arise, how

5 do prescribers and other clinicians change their

6 treatment patterns in response to generic

7 shortages? Both what are the changes in

8 prescribing patterns or, looking at clinicians more

9 broadly, in other ancillary care delivered? What

10 are the spillover effects when there might be a

11 generic shortage?

12 Our group is especially interested in

13 medication adherence. We do a lot of research on

14 chronically taken medications. So when there are

15 generic drug shortages, what are both the immediate

16 and the longer-term effects on patient medication

17 adherence? And do those changes, most importantly

18 from a patient-centered point of view, eventually

19 affect clinical outcomes?

20 All of these findings at the different

21 stages in the process might allow for contingency

22 planning in the event of future medication

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1 shortages which, based on experience, seem like

2 they will continue to arise.

3 Generic drug safety and effectiveness of

4 course is of huge interest to this office, and as a

5 broad topic, the areas in which our division has

6 had interest and that we'd put forward for

7 consideration here. Drug recalls are of course

8 common, occurring nearly once per month.

9 So one of the interesting questions to look

10 at is whether there are specific manufacturer

11 characteristics or other characteristics to help

12 predict which generic medications are most likely

13 to have safety -- that should be "or," not

14 "of" -- to have safety or effectiveness problems

15 when they're on the market.

16 Related to that is the increasing use of

17 compounded drugs as well. So we'd be interested in

18 research on the question of whether compounded

19 generic medications differ in their safety and

20 effectiveness from other generics. Findings from

21 both of these areas could help provide guidance for

22 regulatory policies or safety interventions with

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1 clinicians or with manufacturers.

2 This is some of the research that

3 Dr. Lionberger cited that our group's been very

4 interested in, looking at patient and clinician

5 attitudes, beliefs, and behaviors regarding generic

6 drugs. We've done studies, going back several

7 years, finding that patients and prescribers have

8 some degree of skepticism of generic drugs,

9 although that has been changing over time.

10 One of the areas that we think is

11 interesting, and the kinds of research that we do

12 and the kinds of large datasets to which we have

13 access, are those prescriptions that are written,

14 "Dispense as written," which is often either

15 written by the prescriber or elected by the

16 patient, both of which indicate some degree of

17 skepticism about generic drugs.

18 Identifying prescriber or patient

19 characteristics that predict that decision can help

20 identify areas for educational interventions when

21 that's an avenue that can be used to increase the

22 use of generic drugs.

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

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

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

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

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

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

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

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

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

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

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

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

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1 DR. FISCHER: I have the technology.

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

4 DR. FISCHER: Yes.

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

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

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

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

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

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

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

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

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1 going to talk about product research, if I can do  
2 this. Okay.  
3       So I'm going to argue that the  
4 bioequivalence needs some scientific development,  
5 which is happening now today for the first time.  
6 We need things such as Cmax predictors, AUC  
7 predictors. Remember, bioequivalence is about the  
8 same drug, different products. Same PK. Same  
9 ADME -- same DME, I'm sorry -- different  
10 absorption. So the science of bioequivalence is at  
11 the absorption site. And we need to extend in my  
12 area, oral, to further immediate-release and  
13 modified-release oral dosage forms.  
14       The BCS that started this, I'm going to say  
15 20, 25 years ago, was actually funded by the FDA  
16 25 years ago, when Carl Peck was the Center  
17 Director here. And that's really been penetrating  
18 further and further. And today I'm going to  
19 propose we do subclassification, the next step, I  
20 think, in biopharmaceutics classification.  
21       My thinking when I was working with the FDA  
22 in 1990 -- on sabbatical; they let me out after one

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1 year -- was, some products are simple. Some are  
2 hard. Why? Why? So that led to eventually  
3 categorizing in a classification system.  
4       We now have guidances based on BCS which  
5 allow in vitro biowaivers for BCS Class I drugs, I  
6 think probably principally based because if drug  
7 products dissolve rapidly in the  
8 stomach -- disintegrate, dissolve rapidly -- what  
9 you're measuring in vivo is gastric emptying, not a  
10 product difference. So why do it?  
11       So at any rate, we're continuing to pursue  
12 that line of reasoning and how far we can develop  
13 the dissolution methodology to Class III drugs, II  
14 and IV low solubility drugs, and then modified  
15 release products, which are even more complicated  
16 because of the changing luminal environment along  
17 the intestine, as well as the differentiation of  
18 intestinal cells along the gastrointestinal tract.  
19 So we continue to do studies there.  
20       I think the key science then for oral  
21 delivery, oral product equivalence, is in vivo  
22 dissolution, and I think Dr. Lionberger mentioned

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1 that earlier. What's really happening in the  
2 gastrointestinal tract? Surprisingly, we really  
3 don't have much measurements there, especially  
4 under dosing conditions or our standard  
5 bioequivalence conditions. So we need to look at  
6 the media and methods.  
7       I'm going to propose an in vitro -- I'm  
8 sorry -- in vivo predictive method, dissolution  
9 method, which is not a QC method. That's a  
10 separate science, so that's -- they do a good job  
11 over there for quality control. That's a whole  
12 package for a product. But for product development  
13 we need a dissolution methodology and that would be  
14 useful for things like SUPAC changes, scale-up  
15 post-approval changes, dose scaling, biowaivers,  
16 even QbD and PAT targets for modification of  
17 manufacturing process.  
18       What's your target going to be? Clinical?  
19 Human? No. Way too expensive. We need a better  
20 target, and that would be the in vitro dissolution  
21 for oral products if we had confidence in the  
22 dissolution methodology as representing the in vivo

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1 processes.  
2       So that's what we're in the process of  
3 trying to do at Michigan with various intubation.  
4 I think, again, Dr. Lionberger mentioned this as  
5 one of the FDA contracts where we put a tube here.  
6 In human subjects we measure 15  
7 motility -- contraction; pressure contractions;  
8 different sites, stomach, duodenum, jejunum, ilium;  
9 as well as sample from those four sites.  
10       We aspirate fluid and assay for drug marker  
11 pH, buffer capacity. It turns out buffer capacity  
12 is way much lower than the USP buffer capacity.  
13 I'm not even sure why we call it simulated  
14 intestinal fluid because it's not. But we're  
15 learning things like that, and we're measuring drug  
16 concentration in the intestine.  
17       So we're learning now for the first time  
18 what's really going on between the in vitro product  
19 you're developing, the manufactured product, and  
20 what happens when you put it into the human  
21 subject. We need something in between there. We  
22 don't want to use the human subject as our

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1 experimental apparatus. Right? We think we can do  
2 better. I know we can do better. So that's the  
3 whole process at Michigan.  
4       So we're measuring gastrointestinal  
5 variables during drug absorption, gastric emptying,  
6 duodenal appearance, intestinal transit, various  
7 motility, pH buffer, physical-chemical changes.  
8       One element that we finished in the MRI,  
9 magnetic resonance imaging, to the gastrointestinal  
10 tract, we measured fluid volumes. It's not 900 mL,  
11 which we use in the USP for the apparatus. In  
12 fact, when we give a glass of water, that's all we  
13 see in the stomach, and then it decreases from  
14 there.  
15       In the intestine, total intestine, we see on  
16 average around 70 to 80 mLs, total volume in the  
17 intestine, liquid volume. So how do we develop an  
18 in vitro apparatus? Well, that's what we're in the  
19 process of trying to do.  
20       One point here. Here's the USP dissolution  
21 apparatus methodology for an RLD product,  
22 100 percent in 15 minutes, 50 millimolar phosphate.

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1 That's a USP apparatus. But when you actually use  
2 something that's more physiological -- I'm not  
3 going to make a case that this is, yet, because we  
4 don't have the data -- but it takes 60 minutes to  
5 dissolve in a physiological buffer. Well, how do  
6 we develop a methodology that is reflective to  
7 in vivo? Well, we have to go after the in vivo  
8 data under relevant oral product disintegration.  
9       So I'm proposing BCS subclasses. I'm not  
10 going into that in detail. But I think we need a  
11 product development person. If the drug is an  
12 acid, base, or neutral, that makes all the  
13 difference in the world to what you can do with it.  
14 So I think we need to classify dissolution  
15 methodology, what I'm calling in vivo predictive  
16 dissolution methodology, based on subclasses. And  
17 we're going to have a number of -- maybe 10 or 20  
18 different, maybe more -- dissolution methodologies  
19 that would be predictive.  
20       They're not going to be quality control,  
21 although quality control could be a derivative.  
22 That is, once you decide what's most important for

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1 your product, you could set a quality control  
2 standard. But what we need is a method to help us  
3 decide what is that critical variable, or critical  
4 variables, and then what standard do we set to  
5 ensure that product quality, over time, for both  
6 brand and generics. It's a product standard, not a  
7 drug standard. I mean, the drug is obviously  
8 critical, but it's a product standard.  
9       So the in vivo test is our gold standard, no  
10 question about that. There's no argument there.  
11 We may have to tighten it for narrow therapeutic  
12 index drugs, but I believe that we need to  
13 develop -- and is the in vivo test the best? In  
14 some cases, we know it's not. For BCS Class I  
15 rapidly dissolving, it's not the best test because  
16 the in vivo test tells us nothing. Okay?  
17       So how do we develop a predictive test?  
18 That's what we're in the process of doing at  
19 Michigan now, what I'm calling iPD. In vivo  
20 measurements under typical BE conditions are  
21 clearly needed, which is what we're doing. And  
22 then we can extend the GI measurements based on

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1 non-invasive MRI methods.  
2       That's what we're currently  
3 implementing -- developing the protocols to do next  
4 year, collaborating with the world's expert group  
5 at measuring, by MRI, GI fluids and motility where  
6 we can do it in patients. We can do it in  
7 pediatrics. We can do it in special populations.  
8 So I think we're looking at how we extend these  
9 techniques to patient conditions.  
10       So I think advancing product research in the  
11 21st century is a bigger point that I want to make,  
12 is that for oral we need, of course, in vivo  
13 predictive dissolution methodology. And we need to  
14 measure the GI variables.  
15       But when you think about the type of  
16 products and the list of topics and complex  
17 products, the topics that Dr. Lionberger referred  
18 to this morning were impressive. The range of  
19 issues the FDA has to deal with is enormous, just  
20 enormous.  
21       I think it's maybe incomprehensible to most  
22 of us how many different things, and the expertise

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1 you need to develop a good scientific decision  
2 around the world.  
3 So I think we need, really, a product  
4 regulatory research institute. This is blue sky,  
5 of course, but what do we need to regulate products  
6 for the 21st century when we're seeing all of these  
7 complex products come down the pipe? And where do  
8 we get the expertise to make the best decision we  
9 can make on that product for ensuring efficacy, to  
10 the best of our ability, to patients?  
11 I think I finished on time. Thank you.  
12 DR. LIONBERGER: So I have a question. If  
13 you could only get one -- so in the next year one  
14 new in vivo dataset to help advance in vitro  
15 predictive dissolution, what would it be?  
16 DR. AMIDON: If I could only get one?  
17 Probably MRI.  
18 DR. CONNER: Like yesterday and today,  
19 you've made some side comments as you were  
20 presenting your predictive methods, several times  
21 saying, oh, well, quality control measures, they  
22 don't really need to do this. The FDA --

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1 DR. AMIDON: Be careful. What I  
2 use -- okay.  
3 DR. CONNER: I'm just interpreting what you  
4 say. You can correct me.  
5 DR. AMIDON: I don't want to take down  
6 quality control.  
7 DR. CONNER: The FDA right now is putting in  
8 quite a lot of effort to make their specifications  
9 more clinically relevant.  
10 DR. AMIDON: Yes. Yes.  
11 DR. CONNER: So wouldn't that effort  
12 dovetail with what you're saying, if making all  
13 in vitro -- or making relevant in vitro methods  
14 that predict what we want to know, which is usually  
15 relevant to the patients? So that includes both  
16 bioequivalence or bioavailability plus quality  
17 control, so that you have a spec that actually  
18 means something to the patient and to the  
19 prescriber.  
20 DR. AMIDON: Yes.  
21 DR. CONNER: It's not really that, oh well,  
22 it's no good for predicting what's really going to

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1 happen in people, but it's good enough for quality  
2 control.  
3 You can correct me if I interpreted what you  
4 said is wrong.  
5 DR. AMIDON: No, industry is working on  
6 that. Greg Amidon and myself, we were at a  
7 conference at Lilly three weeks ago on this  
8 particular issue. Lilly, Boehringer Ingelheim,  
9 Merck were there, and AbbVie.  
10 So yes. It is happening in industry, but of  
11 course that tends to be private and proprietary.  
12 So how do we set public standards and to have that  
13 information in public so that it gets an  
14 appropriate vetting? But the answer is yes It's  
15 happening.  
16 What we're developing is based on what was  
17 developed in industry. It's called the artificial  
18 stomach duodenum, ASD. I said to the inventor of  
19 this technology, you don't want to take something  
20 artificial to your boss, do you, unless it's a  
21 Christmas present or something. But at any rate,  
22 yes, so it's happening, Dale, but it's a matter of

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1 the public standards.  
2 DR. LIONBERGER: Thank you very much.  
3 DR. AMIDON: Okay, thank you.  
4 (Applause.)  
5 DR. LIONBERGER: So we will go to our break  
6 now, and we will reconvene about 10:40.  
7 (Whereupon, at 10:22 a.m., a recess was  
8 taken.)  
9 DR. LIONBERGER: Welcome back, everyone. I  
10 just want to let everyone know, we've had some  
11 questions. The slide presentations will be  
12 available on the regulatory science webpage as soon  
13 as possible. We will ask the speakers for  
14 permission before we post them, however, but we  
15 will have those that we have permissions available  
16 as soon as possible.  
17 So again, to continue with our program, our  
18 next speaker is Professor Duxin Sun from the  
19 University of Michigan. So welcome, Duxin.  
20 Presentation -- Duxin Sun  
21 DR. SUN: Thank you very much for the  
22 opportunity of presenting. This represents a group

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1 effort from the University of Michigan. So I will  
2 focus on the BE standard mainly for modified-  
3 release drug product.  
4 So the current BE standard for IR, so  
5 immediate drug release product, works pretty good.  
6 I think mostly work fine. And the challenge is for  
7 the BE study of modified release and a locally  
8 acting drug product.  
9 So of course we still use AUC and a Cmax  
10 comparison, and that's perhaps not enough. Then  
11 for some of the products we use partial AUC to  
12 improve the standard. That's definitely  
13 improvement, but still I think there's still  
14 challenge. I'll show you some of the data what I  
15 mean.  
16 So I will present two ideas. One is one  
17 specific idea to ask, can we add this another  
18 parameter to compare the BE of generic and brand?  
19 And also then I also going to present, once we get  
20 the data, what are the broader implication?  
21 So the question for this specific one is  
22 then I want to introduce this composite appearance

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1 rate. I show the later the data. What do I mean?  
2 The question is, how do we estimate that? How do  
3 we validate that? How do we compare between  
4 generic and brand?  
5 So in the BE study, we use AUC and Cmax  
6 comparison. In here we use a simple -- the  
7 underlying assumption uses simple pharmacokinetics.  
8 So we made a pretty good assumption the absorption  
9 rate -- the absorption is the first order kinetics.  
10 KA is a first order absorption rate constant, is a  
11 constant. We know this is not right and yet we  
12 teach students all the time, for the last 30 years,  
13 because -- that's not because we teach students the  
14 wrong thing, because we have to make  
15 simplification.  
16 For some cases, it does work. For example,  
17 in the oral dissolution case, that's perfectly work  
18 fine. For most immediate-release drug products, if  
19 they are really released, they have dissolution  
20 completed within 30 minutes. They're very similar,  
21 like a solution go down the GI tract. That's also  
22 works fine.

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1 The problem is for local-acting and modified  
2 drug release. So here what I mean is, you can see  
3 this slide is a busy slide. If you have MR product  
4 and local-acting drug product, they may or may not  
5 have a dissolution in the stomach.  
6 Of course, they have structural gastric  
7 emptying. Then you go to GI small intestine. They  
8 also have dissolution release in different region  
9 of the small intestine differently. Of course, you  
10 have a transit.  
11 Then some of the drug may have a  
12 precipitation, and then only the drug dissolving  
13 solution, they are absorbed through the membrane.  
14 So that's we refer to the first order drug  
15 absorption. Even that perhaps is not first order.  
16 I think along the GI tract, they may not be a first  
17 order.  
18 So what I propose to you is another term; we  
19 can use deconvolution, get a composite appearance  
20 rate. Basically, use how fast drug can appear in  
21 the blood, then you can include everything here.  
22 You can include the drug release and the

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1 dissolution in GI tract, precipitation, perhaps  
2 even transit. So I show you how we did it, some  
3 preliminary data.  
4 The question is specifically as applies to  
5 BE, then how do we exactly estimate that? How do  
6 we validate? How do we compare? So what we really  
7 need to do -- the last slide, I will show you what  
8 my proposal is. Here just refresh, is we really  
9 need to measure in vivo drug dissolution and  
10 releasing in human GI tract. So we have done, just  
11 finished the local acting drug product, and we are  
12 currently doing IR drug product.  
13 We really need a one right now is modified-  
14 release drug product for in vivo GI tract drug  
15 release and dissolution. After we get this, we can  
16 get deconvolution from the plasma profile, get this  
17 composite appearance rate based on the plasma  
18 profile compared to oral solution. Then we need to  
19 validating statistical analysis to compare brand  
20 and the generic.  
21 So I'll show you some of the preliminary  
22 data what do I mean. So in Michigan, we have this



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1 technology. We did 60, about almost 100 patient  
2 already for the intubation study. We put a tube in  
3 the human GI tract all the way down from stomach,  
4 duodenum, jejunum, and early ileum. So we cannot  
5 get colon because that's too down there.  
6 Then you can see the different product in  
7 the different location. We get a sample from  
8 different location. We get a GI motility. We get  
9 a pH. We get a structural capacity. Then got  
10 really covered everything together.  
11 I'll show you one piece of the data here to  
12 illustrate my point. So for example, we actually  
13 get a sample. The patient stays there for  
14 overnight but we can do intubation for 7 hours, so  
15 every hour we can get a sample. Then we measure  
16 drug concentration to represent the release and the  
17 dissolution in the GI tract. So you can see we did  
18 Pentasa, Apriso, and Lialda.  
19 So here's the stomach on the very first left  
20 column, and from stomach, duodenum, proximal  
21 jejunum, middle jejunum, distal jejunum, and early  
22 ileum. So you can see from here Pentasa is

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1 released from stomach pretty high level and all the  
2 way from duodenum to early ileum.  
3 Once the surprise is found in here, we never  
4 imagine -- we could actually -- by many years we  
5 can never imagine that the drug concentration stay  
6 in stomach for 7 hours. We always assume they  
7 finish by 2 hours or 30 minutes. Simply is not  
8 true, and we use that assumption for the last -- I  
9 don't know how long, 50 years.  
10 So then what does that mean? What impact  
11 does that have? So that's very surprising. So you  
12 can see this drug release very clear, very  
13 beginning. They release from the very beginning to  
14 the end.  
15 Now, if you compare Apriso, they don't have  
16 a release in the stomach. They have a very tiny  
17 small amount of release from duodenum to jejunum,  
18 then maybe start releasing in late jejunum or early  
19 ileum. That's a very clear difference between  
20 these two drugs, drug product.  
21 If you compare to Lialda, Lialda is designed  
22 to releasing then later, the colon region of the

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1 intestine, but the scale is different. They almost  
2 have zero release, tiny, tiny amount of release, in  
3 early stomach, duodenum, jejunum, ileum. So you  
4 can see they are very different.  
5 So of course then we also get -- for this  
6 study, we also get a plasma concentration. We also  
7 got an oral solution as another arm so we can  
8 compare it to. You can see here the top panel, the  
9 plasma profile Pentasa appraisal. Although I show  
10 you early slide, the GI release is very different.  
11 Their plasma profile, there's some  
12 difference, but if you do it really well, you can  
13 make it bioequivalent based on the plasma profile.  
14 Of course, Lialda is designed differently. They  
15 are very different. You can see the plasma profile  
16 is very different.  
17 So the argument I have is, the plasma  
18 profile cannot tell the difference in terms of GI  
19 release, especially for local-acting drug and for  
20 modified-release drug. However, if you do a  
21 deconvolution to gather this CAR, composite  
22 appearance rate, and the bottom rule, you can

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1 clearly see they are different.  
2 Pentasa in the left lower corner, you can  
3 see release drug from the very beginning all the  
4 way until 10 hours. Then for Apriso, the first  
5 3 hours there's no release, then sharp release,  
6 then perhaps stop release at 10 hours. Then Lialda  
7 is continued release later part.  
8 So those slides tell you two things. One,  
9 the CAR is much more sensitive. We can mirror the  
10 GI real release compared to plasma profile. That's  
11 number 1. Number 2, very surprisingly, everything  
12 seems to stops around the 10 hours. So I'll show  
13 in other datasets. We don't know what that means,  
14 but maybe it means two things.  
15 Number one, for modified-release  
16 formulation, maybe if you make too long after  
17 10 hours, they are never going to be released  
18 because they reach colon. Colon have no water.  
19 Then they don't release. They don't release. They  
20 don't have no absorption. So that's one  
21 possibility.  
22 Number two, so whether it's a release

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1 problem or absorption problem, my guess is perhaps  
2 release problem. So then does that mean in the  
3 future we should not make an extended release more  
4 than 10 hours? I don't know. If that's true, that  
5 has a vague implication.  
6 So I'll give you another dataset. Here we  
7 use 6-week crossover, 6 different formulation,  
8 modified release drug in human. You can see plasma  
9 profile, 2 SR, 2 ER, it's similar. However, again,  
10 the CAR can tell clearly the difference and the  
11 release difference in the three different  
12 formulations. Again, the two points I showed last  
13 slides, these slides also confirmed.  
14 So I think based on those preliminary data,  
15 my proposal would be we don't have any data  
16 currently for modified release drug product in GI  
17 drug dissolution, the release. We have zero. And  
18 we did get the locally-acting drug product. We  
19 will publish that in the next few months.  
20 The ongoing studies for IR drug product, GI  
21 drug dissolution, so we want to get that. We hope  
22 to get another, at a minimum, MR drug release

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1 product. And also then we can estimate and  
2 validate the CAR compared with oral solution, then  
3 validate that by oral GI drug concentration. Then  
4 we need to statistically validate how do you  
5 compare this to a product. How do you use number?  
6 So that's just a specific question. So once  
7 we get those data, then the broader implication  
8 will be we can validate the in vivo predictive  
9 dissolution condition, device, everything, and also  
10 validate all the PBPK modeling, and also cross-  
11 validate the MRI study, the non-invasive MRI study,  
12 for drug transit and motility.  
13 With that, I stop and take of course  
14 questions. Thank you very much.  
15 DR. LIONBERGER: Thank you, Duxin.  
16 Questions? Cindy?  
17 DR. BUHSE: Yes. When you talk about doing  
18 your GI studies with the modified-release products,  
19 different manufacturers often have different  
20 release mechanisms for their modified-release  
21 products. Do you envision having to actually  
22 repeat these complicated clinical trials for all

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1 the different release mechanisms? Or do you think  
2 you can do some, and then do some in vitro work to  
3 try to compare that?  
4 DR. SUN: Yes. So that's a good question.  
5 The idea will be that's not feasible to do the  
6 study as a routine BE standard. That's just way  
7 too slow, way too expensive. The idea is, let's  
8 gather the different class of compound and data to  
9 have confidence. Then eventually the gold standard  
10 has to be blood concentration.  
11 Then how do we use blood concentration  
12 compare to mimic clearly? Ideally, then, we have  
13 datasets to validate all the PBPK model or in vitro  
14 test model. So ideally, we have different  
15 datasets, IR, MR, local acting. So that's the  
16 minimum I say we should have. We don't have any  
17 for last 50 years.  
18 If we want more than that, then perhaps then  
19 different BCS class compound, we need to have each  
20 class compound have a representative, but that's  
21 another few compound. So that's the ideal  
22 solution. But I think if we don't have that much

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1 effort need to go forward, but minimally we should  
2 have an MR drug product to get that down, put in  
3 the public, let everybody use that data to validate  
4 their condition, in vitro condition and model.  
5 DR. LIONBERGER: So when you say absorption  
6 composite appearance rate, do you need some kind of  
7 oral solution to deconvolute that, or is this  
8 something you could obtain from just analysis of  
9 plasma data?  
10 DR. SUN: Ideally, so ideally you have  
11 another arm for oral solution, though, because then  
12 basically you have a brand, generic, and also oral  
13 solution. Then you have an additional arm. In  
14 that way, you can against the oral solution to do  
15 deconvolution, that have a few advantages. Number  
16 one is really to reduce the variability because you  
17 see each individual subject to get rid of our  
18 variability. Number two is really to deconvolute  
19 much more accurately.  
20 Of course, you can also use the literature  
21 data with IV data or other IR release formulation  
22 to do the deconvolution. But that's perhaps

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1 against the average rather than individual. So you  
2 have an advantage and disadvantage.  
3 DR. CONNER: When you use your oral solution  
4 as your baseline for deconvolution, do you pay  
5 attention to how you do the oral solution? Because  
6 we have a tradition of assuming that an oral  
7 solution is uncomplicated. There's no possibility  
8 you can have any change in bioavailability.  
9 But then, quite a few years ago, we came  
10 along with discoveries on things like sorbitol,  
11 where certain drug substances in an oral solution  
12 can be -- their bioavailability can be affected by  
13 excipients, especially -- the alcohol sugars are  
14 the ones we are most familiar with. So don't you  
15 have to take that into account?  
16 You can't just kind of blindly go into that  
17 type of drug and say, oh, any oral solution is  
18 fine, whereas two investigators using different  
19 extemporaneously compounded oral solutions could  
20 come up with very different results.  
21 DR. SUN: True. I think in FDA, the old  
22 days said the oral solution is self-evident.

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1 Right? Perhaps that's not true. A lot of time we  
2 have a precipitation.  
3 So the proposal I have is two things. One  
4 is when we do the intubation, we should also do  
5 oral solution intubation. We know exactly what's  
6 going on. That's actually very valid. Too bad the  
7 data we have, currently have, we're going to  
8 publish, we have a solution arm, but we did not do  
9 the intubation. We thought we don't need it.  
10 So right now, we will look back the data.  
11 We really need an intubation for dosage form and a  
12 solution. Then we get a good idea. The solution,  
13 oral solution, will give you deconvolution because  
14 that will mimic all the transit and everything,  
15 metabolism. I think is actually better, even  
16 better, than IV. You're right.  
17 DR. LIONBERGER: Thank you. So our next  
18 speaker is Chetan Pujara from Allergan.  
19 Presentation – Chetan Pujara  
20 DR. PUJARA: First of all, thank you to the  
21 FDA and Dr. Lionberger for inviting me to present  
22 here. I really appreciate that. And my talk's

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1 going to be on nonbiological complex drugs. And I  
2 want to further highlight -- I think there's been  
3 enough presentations on complex drugs, but I want  
4 to further highlight the challenges in the  
5 assessment of similarity or equivalence of  
6 ophthalmic emulsions.  
7 A real quick declaration of interest from  
8 the NBCD working group. I'm not going to read  
9 through this. It will be part of the slides that  
10 will be posted. So I'll move on.  
11 So the outline of my talk, I'll quickly  
12 introduce what nonbiological complex drugs mean.  
13 And then we'll talk about emulsions as complex  
14 dosage forms. And I feel strange standing in front  
15 of Ken Morris and Steve Byrn and others talking  
16 about emulsions. They're the ones who taught me  
17 all this. And I'll spend a little bit of time on  
18 assessment of similarity and equivalence of  
19 ophthalmic emulsions.  
20 So I think there's good recognition that we  
21 have small molecule drugs, tablets, capsules,  
22 et cetera, that are formulated, and we have

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1 biologicals that are considered complex drugs.  
2 More recently the term -- or yes, I guess the term  
3 nonbiological complex drugs is starting to gain  
4 popularity. There was an article also published on  
5 this.  
6 At a very high level, NBCDs constitute of a  
7 multitude of closely related structures. The  
8 entire complex is the active pharmaceutical  
9 ingredient. I think Dr. Amidon mentioned earlier  
10 it's not just a drug, it's the drug product.  
11 The properties cannot be fully characterized  
12 by physical-chemical analysis. And it was good to  
13 see Dr. Lionberger talk about Q3, talk about  
14 microstructure analysis. The well-controlled,  
15 robust manufacturing process is also fundamental to  
16 reproduce the innovator's product. And that's  
17 something I want to further emphasize as we go  
18 through the few slides that I have.  
19 So with respect to assessment of similarity  
20 or equivalence for nonbiological complex drugs, we  
21 believe that new knowledge and policies need to be  
22 created. I think practically everyone in this room

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 link in these guidances to in vivo performance is  
2 still missing. And it's also deficient in details  
3 on how robust these characterization methods need  
4 to be.  
5       What I mean by that is several years ago, I  
6 think, when I was part of PQRI, we published  
7 particle size methodology and we indicated how  
8 different particle size methods can give you  
9 different results. And this was just for solid  
10 particles.  
11       If you take an emulsion, as I showed the  
12 little cartoon there, it's malleable, and the  
13 characterization methods can affect how these  
14 emulsions will perform in the method. So both the  
15 sampling characteristics and the way the emulsion  
16 is measured, or determine the particle size, will  
17 be affected by the instrument, but also the  
18 parameters that are used much more than, I would  
19 say, a solid particle.  
20       So what that leads me to say is, and we have  
21 obviously done some research on this, that we can  
22 take disparate emulsions and show that they are

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1 similar just by changing the parameters with which  
2 one can determine the particle size. So the  
3 robustness of these characterization methods is  
4 very important.  
5       Further understanding of locally-acting  
6 ophthalmic emulsions is necessary to create  
7 scientifically robust guidance with respect to  
8 assessment of similarity or equivalence of  
9 ophthalmic emulsions. We believe that. So I would  
10 submit to the panel here that research in the  
11 following areas would be a good first step.  
12       In vitro drug release methods that can be  
13 linked to in vivo performance -- I think we've  
14 already heard a couple of talks on this earlier  
15 today, and probably more to come. I saw Diane's  
16 topic. She's going to talk about in vitro-in vivo  
17 methods and how we can link them.  
18       With respect to ophthalmic dosage forms,  
19 it's even more critical because it's locally  
20 acting. There are no methods, as far as I know,  
21 that are available. And most of the methods  
22 basically take a 900 mL dissolution bath and they

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1 try to miniaturize it, and I don't think that's  
2 probably sufficient.  
3       So this is an area that's ripe for research.  
4 And I'm looking at all the great professors sitting  
5 in the front here, and I would submit that a lot  
6 can be learned here to make better drug products  
7 available to patients.  
8       Then, as I mentioned earlier, robust  
9 emulsion characterization methods, research in this  
10 area would also be a good first step -- for  
11 example, drug distribution. And in the recent  
12 update to the guidance, I noticed that that's there  
13 in terms of how the microstructures can affect.  
14 Droplet size I already talked about. And of  
15 course, the intention of developing better methods  
16 is to provide meaningful information on impact of  
17 in vivo performance.  
18       So with that, I have four seconds remaining.  
19 I will stop and thank the panel, and take any  
20 questions.  
21       DR. LIONBERGER: Thank you. So in terms of  
22 the in vitro release method, what do you think are

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1 some characteristics of a good in vitro release  
2 method for an ophthalmic product? And to your  
3 knowledge, do any of the approved brand products  
4 have good in vitro release methods?  
5       DR. PUJARA: Yes. That's a very good  
6 question. I'm not aware of any good in vitro  
7 methods in the ophthalmic area. You're absolutely  
8 right. Typically, companies would use in vivo  
9 methods to further understand because we can get an  
10 assessment of both tolerability of the dosage form,  
11 because this is a locally-acting drug, and we can  
12 understand in which tissues these drugs are going  
13 into.  
14       We've not spent much time in developing  
15 in vitro methods because this is an area that I  
16 think is -- I think we need some disruptive  
17 technologies to further advance the science in this  
18 area, and we haven't invested a whole lot in it.  
19 However, as I mentioned, for development purposes,  
20 we typically do use in vivo methods.  
21       DR. LIONBERGER: Thank you very much.  
22       DR. PUJARA: Great. Thank you very much.

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1 DR. LIONBERGER: So our next speaker is  
2 Professor Catherine Sherwin from the University of  
3 Utah.  
4 Presentation – Catherine Sherwin  
5 DR. SHERWIN: Good morning, everyone. And a  
6 slight change of topic and a slight change of  
7 direction for my talk, but hopefully very of  
8 interest to everyone, and also very relevant to me  
9 in my research group. I want to talk about issues  
10 associated with children and generic drugs. I have  
11 nothing to disclose.  
12 Some things that we're concerned about,  
13 those of us who work in pediatrics and pediatric  
14 clinical pharmacology, is what are the differences  
15 between the generic drugs and the brands. And I'm  
16 a big fan of generics. I'm an advocate for them.  
17 I think they are needed, vitally needed. But in  
18 some circumstances in pediatrics this is becoming  
19 very difficult with regards to the clinical  
20 perspective, the parents' perspective, and then  
21 also the perspective of the child.  
22 So is it always good that these are cheaper

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1 and always available? Are they just as good? And  
2 we've heard lots of very in-depth scientific  
3 presentations yesterday and also this morning about  
4 oral absorption. And in that circumstance, are we  
5 considering differences in maturation within  
6 children and their different maturation of the  
7 gastrointestinal system?  
8 So can we maintain the quality and reduce  
9 healthcare costs if we use more generics? And I  
10 think we can. I just think we need more  
11 consideration, particularly on the pediatric side.  
12 So what criteria should we have for  
13 switching from brand to generic drugs, particularly  
14 in a pediatric population? And do we have a  
15 therapeutic switch? And if we do these, how do  
16 they differ and is this relevant for that patient  
17 population?  
18 So the generic approval differences are  
19 available within the brand drug. For pediatric  
20 indications, they usually test in adults first, and  
21 this is obviously due to ethical considerations and  
22 constraints. We can't get a child, line up a whole

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1 bunch of children, and tell them to volunteer to  
2 take a drug that they don't need and they won't  
3 need. I can't see many parents consenting to see  
4 that happen.  
5 Also very difficult to take the number of  
6 blood samples that we need to look at the PK within  
7 that patient population. So we are definitely  
8 relying on the information that comes from adults.  
9 Bioequivalence is based on kinetics and the  
10 pharmaceuticals. We've heard about dissolution.  
11 We've heard about absorption. These things vary in  
12 children. They vary in the neonatal population.  
13 They vary between ages of children and between a  
14 child that's a 2-year-old versus a 10-year-old. So  
15 does this mean that we need to look at differences  
16 in repeating assessments for steady states of drugs  
17 within children? And how do we compare the  
18 therapeutic effectiveness between drug A and drug B  
19 within this patient population?  
20 So we do a lot of bioequivalence evaluation  
21 study design. We have very set, very specific  
22 criteria to achieve that. It's done very

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1 standardized within the Office of Generic Drugs.  
2 There's a lot of opportunities, and Dr. Lionberger  
3 outlined this morning all the initiatives that are  
4 being done. They do careful controlled crossover  
5 studies. We do comparisons between the brands of  
6 the generics.  
7 The patients typically are young, healthy  
8 adult and mainly male, and definitely not in the  
9 pediatric realm. We're looking at comparisons  
10 between AUC, Cmax. We look at measurement, and we  
11 look at the half-lives between those patient  
12 populations.  
13 We know within pediatrics those half-lives  
14 for many of these drugs actually vary. And  
15 depending on the age of the child, we have a  
16 variability in clearance. We have a variability in  
17 absorption.  
18 So it becomes very difficult when you're  
19 trying to equate these from an adult population  
20 across into pediatrics. We typically, in the adult  
21 population doing crossover designs, look at  
22 different half-lives. And all of those becomes

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

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

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

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

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1 the obesity epidemic grows and these children are  
2 developing cardiac conditions. We're using cardiac  
3 drugs that have never been tested in children.  
4 Antidepressants, the same, being used in  
5 younger, younger children where we've never done  
6 these clinical trials or done these clinical  
7 studies. Other areas of concern -- transplants and  
8 oncology and a lot of drugs that we're using in  
9 those that we're extrapolating the data from adults  
10 and using them down in pediatric patients.  
11 Generics have a role. As I say, I am a fan  
12 of generics in pediatric medicine. They are  
13 desperately needed, particularly within the  
14 underserved populations, and for these children to  
15 have access to this medication. But we need to  
16 have consideration for this.  
17 We need to look at the reduction in medical  
18 costs as being a benefit, and again, that was  
19 covered earlier this morning. But we also need to  
20 look at any unanticipated health costs which can  
21 come when we use these drugs in a pediatric  
22 population where we have no clinical information,

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1 where we don't have this information to know the  
2 differences.  
3 There's few studies done in pediatrics where  
4 we compare drug A and drug B, much less looking at  
5 cost-effectiveness. And is it cost-effectiveness  
6 in some of these cases to change a child from a  
7 brand drug to a generic if we know that they may  
8 have an increased likelihood of an adverse event?  
9 Without pediatric studies about the  
10 pediatric label, we have the exclusivity which the  
11 FDA brought in through the BPCA and the FDAMA a few  
12 years ago, which has made a big change to industry  
13 having to do some of these pediatric studies.  
14 But we still don't have as much information  
15 as we need within this population. So generic  
16 switches are seldom based on pediatric data. It's  
17 usually the data that's been gathered from adult  
18 studies.  
19 So in my summary, I am an advocate of doing,  
20 obviously, pediatric research. I would like us to  
21 be able to use the data that we currently have  
22 available. Again, as Dr. Lionberger said this

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1 morning, we have data in these electronic medical  
2 records. We have data in these insurance claim  
3 bases. We have modeling and simulation which we  
4 can use. We can extrapolate the data. We can do  
5 models. We can take the data from the adult side  
6 and extrapolate it down to children.  
7 But I'd like us to look more at the  
8 differences between the innovative and generic  
9 drugs and how this affects substitutions within  
10 this patient population. How do we distinguish  
11 between a therapeutic and a generic substitution  
12 when treating children?  
13 How do clinicians make that decision? How  
14 do the pharmacists who are filling the scripts make  
15 those decisions? How can we identify the general  
16 factors to consider for a therapeutic switch and a  
17 generic switch?  
18 I think there's a lot of innovations that  
19 the FDA, through their granting mechanisms, are  
20 actually starting to try and look at these things.  
21 And I think this is something that we really need  
22 to be doing, and not only in pediatric population,

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1 but also within pregnant women, breastfeeding  
2 women, and geriatrics as well.  
3 My last point is to select therapeutic areas  
4 for generic substitution increase of adverse events  
5 and to look at those more closely so that we can  
6 prevent those worse outcomes from occurring. And  
7 that would be me.  
8 DR. LIONBERGER: Thank you. Questions?  
9 DR. STODART: Thank you for your  
10 presentation. In general, do you see any  
11 particular age range or ethnicity that is more  
12 vulnerable than others?  
13 DR. SHERWIN: So the age range that, from my  
14 perspective that is the most vulnerable is the  
15 neonatal age range and the under the age of 2. And  
16 ethnicity, I live in Utah and I work in Utah, which  
17 is a very homogenous population.  
18 But definitely within the studies that we  
19 do, we see issues in the Pacific island population  
20 and also in the Native American Indian population  
21 within our region. And that's most of my  
22 experience in America.



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1 DR. LIONBERGER: When we talk about  
2 differences between the brand and generic, as  
3 Gordon has mentioned, it's really a product  
4 formulation that's different. And I think a lot of  
5 the -- some of the discussion things like  
6 clearance. Right?  
7 You don't think that the clearance of the  
8 active ingredient is going to be any different in  
9 whichever patient the product is given. So can you  
10 identify the specific product differences that you  
11 think are of concern for substitution in different  
12 populations?  
13 DR. SHERWIN: So the one that we've done the  
14 most research on, and one actually which we have a  
15 grant through your office right now, is looking at  
16 the immunosuppressants and looking at tacrolimus.  
17 And we have identified some differences in the very  
18 younger age group patients, around 2-year-olds.  
19 Above that, it does tend to equvalate to  
20 adults. But it's definitely in that 2- to 3-year-  
21 old range that we do see differences, which is  
22 obviously related back to maturation within that

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1 patient population.  
2 DR. CONNER: Could you give a little bit  
3 more detail on the differences? And I won't go to  
4 therapeutic substitution, which is not a generic  
5 drugs issue, because that's a substitution that's  
6 made by the physician by writing a new order, a new  
7 prescription.  
8 So it has all of the medical monitoring that  
9 any other prescription would have but the generic  
10 substitution, which does not necessarily involve  
11 the physician, but is done at the pharmacy or  
12 institutional level.  
13 Also I'd like your ideas on if, you know for  
14 the generic substitution or generic products, if  
15 you feel that there isn't enough information in  
16 pediatrics, what would your suggestions be about  
17 going and getting it? Knowing that the generic  
18 product, when it comes in as a new application, has  
19 probably never been --  
20 DR. SHERWIN: Never been used.  
21 DR. CONNER: -- published or seen or is the  
22 world literature. It's a brand-new formulation

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1 that is attempting to copy, in a way, the existing  
2 product that's hopefully very successful in  
3 patients in the marketplace.  
4 DR. SHERWIN: So something that we see  
5 within our institution is, particularly for one of  
6 the studies that we're doing right now, looking at  
7 Botox for children with muscular spasticity.  
8 We've seen, actually, a difference in  
9 adverse events within the difference between the  
10 brand and the generic. So there's something that  
11 we're seeing within a pediatric population that  
12 hasn't actually been seen much in adults.  
13 We've been looking at other specifics and  
14 other drugs that we see differences in. Some of  
15 the antibiotics that we see used within our younger  
16 patient population is different to what we see in  
17 our older patients. So within our neonatal  
18 population, things like vancomycin, we see a  
19 difference within the kinetics, depending on  
20 whether the doctors are ordering the brand versus  
21 the generic. And we have had reports from our  
22 doctors.

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1 The way that we have been addressing this is  
2 actually pulling data from our large electronic  
3 data warehouse. And we pull information on whether  
4 the patient had the brand, whether they had the  
5 generic.  
6 We look at the outcomes. We look at when  
7 did they switch? Why did they switch? What were  
8 the differences? What were the indications? Was  
9 there a therapeutic reason to switch? Was there a  
10 concern from the patient about which drug they were  
11 on?  
12 It's hard for us. We don't actually work on  
13 the outpatient side, where I think there's actually  
14 probably a lot more of these concerns within the  
15 patient population from parents. And we do get  
16 that back through our patient pharmacy therapeutics  
17 committee, but we don't see it much. I see more  
18 the inpatient side.  
19 DR. CONNER: It seems to me some of the  
20 examples you just cited were injectables.  
21 DR. SHERWIN: Um-hmm.  
22 DR. CONNER: The vancomycin, I assume you

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1 mean the injectable use of vancomycin.  
2 DR. SHERWIN: Um-hmm.  
3 DR. CONNER: Another one, the Botox, I think  
4 is an injectable as well.  
5 DR. SHERWIN: Um-hmm. Injectable, yes. IM.  
6 DR. CONNER: So a generic of that would be  
7 virtually identical as far as its inactive  
8 ingredients.  
9 DR. SHERWIN: Um-hmm.  
10 DR. CONNER: The active ingredients -- I  
11 think the Botox is a somewhat complex drug  
12 substance.  
13 DR. SHERWIN: Yes.  
14 DR. CONNER: So your problem, if it exists,  
15 could be there. But as far as generics go, they're  
16 essentially a very simple approach of trying to  
17 copy, literally copy --  
18 DR. SHERWIN: Copy.  
19 DR. CONNER: -- an injectable point by point.  
20 DR. SHERWIN: Yes.  
21 DR. CONNER: Unlike some oral products,  
22 where you have different excipients.

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

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

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

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

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1 I think it is work in progress, and we need to do  
2 more in that area.  
3 I think the point that -- Dale Conner asked  
4 that question; I want to hone in on that question  
5 to frame the talks that NIPTE wish to share with  
6 you -- is clinical relevance of QC methods. We  
7 cannot ignore that question. It is part and parcel  
8 of everything we do. And every method we may  
9 develop for bioequivalence, there is a built-in  
10 assumption that the product you're using is the  
11 right product for that method.  
12 What we have learned, especially -- Gordon  
13 is not here, but Gordon, before Dr. Amidon's  
14 sabbatical, I was with him at FDA then. The  
15 advantage we had was, we had the biopharm filing  
16 room right next to my office. We were able to  
17 review every NDA application that was submitted for  
18 the BCS guidance finalization.  
19 What we found was that dissolution is  
20 product-specific, formulation-specific. Seventy  
21 percent of the time it's over-discriminating, but  
22 30 percent of the time it's not. And the

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 identified. Isn't there a better way of dealing  
2 with that and integrating the formulation science  
3 aspects to this?  
4 I think I had an opportunity to guide a  
5 client through the first approval of the nasal  
6 spray product that I'm talking about. I think this  
7 is the right question, the right time, can be  
8 significant benefit here.  
9 So I think need for integration and clarity  
10 is important from these aspects. And I will skip  
11 through a number of things to go back to the  
12 summary slide, maybe, to think about the totality  
13 of efforts that need to go in.  
14 I think the regulatory science agenda,  
15 really, if you -- I request you to consider  
16 locating a portion of your funding and  
17 prioritization to knowledge base and standards for  
18 integration development across the product class  
19 categories that you have.  
20 I really would leave it at that to say that  
21 to achieve the public health objective of first  
22 generics right on time, right question at the right

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1 time is necessary. One voice of quality. And we  
2 believe the missing element here is the integration  
3 and knowledge management that needs your  
4 consideration. Thank you  
5 DR. LIONBERGER: Thank you very much.  
6 So can you clarify a little bit about what  
7 types of knowledge you'd see in this?  
8 DR. HUSSAIN: Sure. I think immediate high  
9 priority in terms of that would be what we have  
10 been looking at. Just based on your research, I  
11 think you're looking at Q1, Q2, Q3 aspects. And  
12 actually moving away from Q3 aspects for inhalation  
13 and so forth are important.  
14 So the knowledge base that is missing there  
15 is the excipients. Our excipients are controlled  
16 based on certificate of analysis that actually do  
17 not tell you anything about the functionality.  
18 Therefore, in knowledge base of excipients and how  
19 to use those excipients in those settings would be  
20 important.  
21 I think excipient knowledge base is  
22 important all across, but one can prioritize to the

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1 high areas and then think about that. We tend to  
2 focus on excipients only in terms of oral, but  
3 excipients get more and more important for topical,  
4 inhalation dosage form and so forth. That would be  
5 one area.  
6 The other area, really, I think, from  
7 knowledge management is, I think, what are the  
8 right questions to be asked at the right time? I  
9 think, given that we are using more analytics,  
10 especially, I think, if I look at my thought  
11 process in helping Sandoz go through first in/last  
12 out. We have to use orthogonal analytics to  
13 characterize the RLD and show similarity. Those  
14 analytics are above and beyond those of compendial  
15 and other trace requirements. That opens companies  
16 and FDA vulnerable to challenge, continued  
17 challenge.  
18 So what is the right knowledge base  
19 of -- what knowledge base guides us through what  
20 are the right analytics and how do we address that,  
21 is another example. But I think integrating the  
22 pieces together is something we struggle. We often

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1 tend to be focused on one particular area. Cutting  
2 across and connecting the dots across multiple  
3 disciplines is a challenge, and I think we can do  
4 some significant focused efforts there.  
5 DR. BOAM: Do you have any thoughts about  
6 how to make this knowledge base visible to  
7 everybody in the sense that for standards we have  
8 our guidances, or we have it at the USP or ASTM?  
9 Obviously, for knowledge we've often relied  
10 on publications, the literature, I would say. But  
11 how would you envision making knowledge a little  
12 bit more transparent, maybe? Or what's important  
13 the literature and what isn't, or et cetera?  
14 DR. HUSSAIN: I think literature clearly is  
15 part of the knowledge base, but it's not  
16 sufficiently specific to help guide informed  
17 development and other decisions. Draft  
18 guidances -- guidances are knowledge summaries.  
19 And if I simply make an -- to take an example, that  
20 every dissolution method you recommend in your  
21 draft guidance is formulation-specific, is derived  
22 from that of the RLD or what's in the USP, the

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1 generic industry has no choice but to use that as a  
2 target. Then they stop thinking about, is that  
3 method specific to this formulation? Or my  
4 formulation would be dealt with that.  
5 So if we can think about your draft  
6 guidances, if you can think about a summary  
7 scientific assessment, scientific knowledge base  
8 that could be a white paper that gets associated  
9 with that, it could be specifically targeted for  
10 each of those guidances. What are the other  
11 scientific considerations?  
12 Or it could be, I think, as Ken Morris will  
13 talk about that in more detail, is it could be  
14 computerized information system which has the  
15 repository of data, but also the rules of what are  
16 the questions to be asked, what's the logic, and  
17 going in the direction of an expert system also.  
18 So there are different ways of looking at  
19 that. And where you start from and where we want  
20 to go will depend on, I think, what topic we choose  
21 to work on that.  
22 DR. LIONBERGER: Thanks very much, Ajaz.

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1 So our next speaker is Professor Stephen  
2 Byrn from Purdue University, also representing  
3 NIPTE.  
4 Presentation – Stephen Byrn  
5 DR. BYRN: Thank you very much. I'm going  
6 to try to embellish on some of the questions that  
7 were just asked, really, one about knowledge  
8 management and one about specific areas of  
9 investigation. I'm also going to try to hit a high  
10 point on the pediatric formulations.  
11 So the overall title of this part of the  
12 NIPTE presentation is, "A Mechanism for an  
13 Integrated Approach of Formulation Research,  
14 Knowledge Management and Knowledge Sharing, being  
15 proposed and advanced by NIPTE."  
16 We don't probably need to spend tons of time  
17 on this slide. This slide is just highlighting a  
18 complexity of formulation science. On the one  
19 hand, we have performance issues, reliability,  
20 formulation stability, bioavailability, safety, and  
21 then on the other hand, we have processes.  
22 The design of the formulation, I think, is a

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1 critical element. Characterization, we talked  
2 about analytical recently. Prior knowledge in the  
3 literature and in scientific meetings. And then  
4 all of the approval and compliance decisions that  
5 come into play. So all these combined, obviously,  
6 as we've been talking about, make it a very complex  
7 area.  
8 The issues are broad, and the ones I'm going  
9 to try to talk about relate to fundamental  
10 understanding, and specifically the bullets, the  
11 ones with the lines. The structure, obviously I'm  
12 going to try to hit solid state chemistry,  
13 reactions that can occur, as well as the components  
14 like the excipients. And then the design, the  
15 entire design of the formulation, structure,  
16 performance, behavior, all of those issues.  
17 Listed with the bullet points are four areas  
18 of a special concern, the idea that acid-base  
19 reactions can occur, especially with drugs and  
20 excipients; the whole nanoparticle field; emulsion  
21 formulations that Dr. Pujara already covered; and  
22 control of these complex formulations.

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1 Just some additional issues. Pediatrics,  
2 stability, failure modes are often not fully  
3 explored. We've been doing quite a bit of failure  
4 mode work in the abuse-deterrent area, but still  
5 generally they're not fully explored. And then  
6 Dr. Morris is going to cover the question-based  
7 review and the right questions at the right time.  
8 So this slide is a summary of what I'm going  
9 to present in the next few slides. It highlights  
10 complex or problem formulations that we know about.  
11 It's a lesson that can lead us to more  
12 understanding as we go into the future. We don't  
13 want to forget about history, is what I'm saying.  
14 So on the controlled release side, we've got  
15 both the bupropion, Wellbutrin, which we've already  
16 heard a little bit about, and the methylphenidate  
17 area.  
18 On the emulsion-base formulations that have  
19 already been covered, we had the pretty well-known  
20 Neoral situation. We have the nanoparticle side.  
21 And then there's tremendous interest in BCS  
22 Class II, using the old system of formulations of

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1 those products, because those, especially in the  
2 antiviral area, those are tremendously important  
3 products. And of course, we're curing some  
4 antiviral diseases now with BCS Class II products.  
5 And then I already mentioned failure mode.  
6 So I'm going to go into some specific  
7 historical examples. Some of these have been  
8 addressed earlier, and these are quite interesting.  
9 This is the Neoral case. And you can see the first  
10 vial on the left is Neoral in water. And a second  
11 vial is another product in water. And you can see  
12 the particle size is tremendously different in  
13 those two vials.  
14 This reminds me of a quote from Yogi Berra  
15 where he said, "I can observe a lot by just  
16 watching."  
17 (Laughter.)  
18 DR. BYRN: Okay. So we can see a lot about  
19 the particle size by just watching these two. And  
20 if we got to apple juice, you see the same, a big  
21 difference. And then more similarity in the last  
22 two vials.

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1 Clearly, there's a structural particle size  
2 variation of the type that Dr. Pujara was talking  
3 about. We need to understand that better. We need  
4 to understand how those formulations are performing  
5 and what role the particle size. And Dr. Morris  
6 will talk about QbR related to that.  
7 This is a famous bupropion/ Wellbutrin case.  
8 In that case, one thought is that it's structurally  
9 related to the two different formulations. The XL  
10 300 bupropion dose-dumped, whereas the Wellbutrin  
11 formulation, which was made by different technology  
12 and had a different structure, the membrane  
13 technology did not dose-dump.  
14 Again, QbR questions in that area and just  
15 specifically trying to figure out what the  
16 structure of those two formulations are, the  
17 manufacturing, and how those parameters lead to  
18 different behavior.  
19 Here is one on the pediatric side. This we  
20 found in a magazine in one of our children, when we  
21 took one of children to the doctor. We found this  
22 ad in a magazine. And here we have a young lady.

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1 I guess she's about 10 or 12. And the ad is quite  
2 interesting.  
3 These are two products now. They're  
4 bioequivalent, Metadate and Concerta. And what  
5 they're advancing on this ad is that the Metadate  
6 is better blood levels in the critical learning  
7 areas. So it's again -- and these two are  
8 structurally different formulations. The Metadate  
9 is beads, coated beads, and the Concerta is an oral  
10 formulation.  
11 Of course, there's tremendous -- there has  
12 been historically quite a bit of internet traffic  
13 on which of these formulations work best in adult  
14 ADHD patients. And perhaps it's related to these  
15 levels.  
16 This is not a scientific study, it's an  
17 advertising study, but it's pretty interesting to  
18 see what people are advancing as different blood  
19 levels from different structures of formulation.  
20 Just a structural difference in the way they work,  
21 really.  
22 Here's the famous ritonavir case.

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1 Ritonavir, a very important anti-HIV drug, the  
2 Magic Johnson drug, crystalized in Form II. After  
3 a year and a half on the market -- this is about 15  
4 years ago, and had to be -- the original  
5 formulation had to be withdrawn, and there was  
6 about a year delay. And if we go through, I'm  
7 sorry this isn't a very good picture on the right,  
8 but it's similar to that Neoral case.  
9 The bottom flask is the magic surfactant  
10 that creates -- when you dissolve this formulation,  
11 it creates a clear solution, which would be very  
12 small particle size. The top two vials, or  
13 Erlenmeyer flasks, are dissolution experiments  
14 where the product results in an opaque solution,  
15 again similar to the Neoral.  
16 The bottom product is purported to be better  
17 and gives higher blood levels. And there's a lot  
18 of discussion about precipitation in the GI tract  
19 and so on. Again, a very complex formulation  
20 that's even affecting precipitation in the GI  
21 tract.  
22 Finally, just a quick picture. This is a

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1 picture of Abraxane, a very important drug for  
2 breast cancer. Completely cartoon. From what I  
3 can tell in the literature, we don't know what the  
4 structure of that particle is, but this is an  
5 advanced concept of what the structure might be.  
6 Again, there will be generic products to Abraxane  
7 in the future, and we need to know more about that  
8 product.  
9 I'm going to skip this one and go to a  
10 conclusion. Here's my summary slide. So I've been  
11 trying to address the mechanism for an integrated  
12 approach. And down at the bottom bullet are some  
13 deliverables that we believe NIPTE can bring to  
14 bear, and it was related to some of the questions.  
15 How are we going to develop this scientific  
16 information? One would be either targeted white  
17 papers or publications, "what if" scenarios,  
18 scenario based research, transdisciplinary  
19 elaboration to inform question-based review; and  
20 then, two key elements -- a training program, and  
21 we envision NIPTE to become the curated knowledge  
22 base for formulations, probably a web-based system,

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1 although this is evolving.  
2 So I'll stop right now. And again, thanks  
3 very much for inviting me.  
4 DR. LIONBERGER: Thank you.  
5 DR. UHL: Could you expand a bit more about  
6 the knowledge base aspect? I know Cindy had a  
7 question, too. So what I heard -- because I  
8 appreciate you mentioning -- what you just said  
9 expands a little bit on what Ajaz just said.  
10 DR. BYRN: Right.  
11 DR. UHL: Because I'm trying to wrap my head  
12 around, what would that look like? Who would own  
13 it? How would it be available? These are just --  
14 DR. BYRN: Sure.  
15 DR. UHL: How would you get the data to  
16 populate in the first place? So if you could  
17 just -- any kind of thinking you guys have related  
18 to this.  
19 DR. BYRN: Sure. And other people can  
20 elaborate on this, and it's an evolving concept.  
21 We're academics, so we're open literature  
22 production. So we view it would be open. It could

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1 be on a website, like the pharmaHUB. It would be a  
2 combination of white papers, studies.  
3 I can't get out of my head the idea that  
4 therapeutically, like the conazoles -- so all that  
5 antifungal conazoles, I can't get it out of my head  
6 that those formulations might be somewhat similar.  
7 So one structure would be based on drugs that hit  
8 certain targets. We would classify those all  
9 together, and we would have a white paper or  
10 something on formulations.  
11 On the emulsion side, we would break from  
12 that and go straight to emulsions, I think, like  
13 Dr. Pujara proposed. So we would have -- and  
14 Dr. Munson is going to talk about analytical  
15 strategies. For example, NMR is very powerful for  
16 emulsions. So that would be an aspect also. So I  
17 could envision white papers in these different  
18 areas, but I think this is all evolving.  
19 DR. UHL: Okay. Thank you.  
20 DR. LIONBERGER: In your talk, you have a  
21 bunch of somewhat older examples of product issues.  
22 What do you think -- how do you think this

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1 knowledge base would address the -- prevent or  
2 address those type of, say, formulation failures  
3 that you tried to illustrate?  
4 DR. BYRN: Sure. Especially in the emulsion  
5 area, like Dr. Pujara said, we don't know where the  
6 drug is, even. Is it in the oil droplet? Is it in  
7 the micelle? Between the components and the  
8 micelle? As he pointed out, it's equilibrating,  
9 potentially. What controls the particle size of  
10 that material? All of that is critical I think.  
11 So we would address all of those issues.  
12 I think some of these old ones that I showed  
13 probably we know more about, but certainly in the  
14 emulsion side we don't know much more. And I don't  
15 think we know much about the nanoparticles, either.  
16 DR. CONNER: One of your examples, you made  
17 the statement that Metadate CD is bioequivalent to  
18 Concerta, I believe. That's simply not true.  
19 DR. BYRN: Okay. Okay, great.  
20 DR. CONNER: It's not rated that way. And I  
21 was checking the orange book just to make sure that  
22 my memory is --



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

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

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

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1 (Laughter.)  
2 DR. UHL: So to expand on that  
3 though -- because, Ruth, that's a good question.  
4 And your answer was FDA and industry.  
5 DR. BYRN: Yes. Yes.  
6 DR. UHL: Those are two huge buckets.  
7 DR. BYRN: Right. Exactly.  
8 DR. UHL: So do you have more targeted ideas  
9 or --  
10 DR. BYRN: Well, we have a hundred profs in  
11 NIPTE, so we think we have capacity to handle quite  
12 a bit. But our strategy would be to start small  
13 and maybe start a few buckets and build up.  
14 DR. LIONBERGER: All right. Thanks.  
15 Anyone? I think it's time for lunch. We will  
16 reconvene at 1:00 p.m. for the afternoon session.  
17 (Whereupon, at 12:02 p.m., a lunch recess  
18 was taken.)  
19  
20  
21  
22

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1           AFTERNOON SESSION  
2                   (1:01 p.m.)  
3           DR. LIONBERGER: Welcome back, everyone, to  
4 our afternoon session. It's my intention to start  
5 on time, end on time. I know it's Friday  
6 afternoon, and if you didn't get a chance to go  
7 outside, it's a beautiful day outside. I hate to  
8 tell you that, but --  
9           So our first speaker for the afternoon  
10 session is Professor Ken Morris from Long Island  
11 University, also representing NIPTE. So welcome,  
12 Ken.  
13           Presentation – Kenneth Morris  
14           DR. MORRIS: Thanks, Rob. Good afternoon,  
15 everybody, and thanks very much for the invitation,  
16 Rob and NIPTE. So I'm going to continue discussing  
17 some of the themes that Ajaz and Steve discussed  
18 before break, but drilling down a little bit more.  
19 And this is still focusing on the idea that QbR is  
20 really an organizing principle that I'll try to put  
21 in context of the larger theme that we've been  
22 discussing.

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

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

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

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1 questions, good questions, about the  
2 training -- but we had done training for PAT when  
3 the PAT guidance came out. We had done unit  
4 operation training; Chetan Pujara was part of that  
5 at the time. And those were very successful  
6 groups. And I think the premise should be  
7 included, or should persist, but there are other  
8 mechanisms by which we can share knowledge as well.  
9 Let me give you the example I was talking  
10 about. So this is from -- there were a couple of  
11 advisory committees we had when I was on ACPS on  
12 levothyroxine. And this one just highlights the  
13 fact that for levothyroxine, there was a very small  
14 window. It's a narrow therapeutic index compound  
15 by classification, that is, pharmacologic  
16 classification. And very small changes in the  
17 potency would potentially cause very large changes  
18 in the patient outcome.  
19 So Eric Duffy had compiled all the data.  
20 And you can see that between manufacturers, as well  
21 as within manufacturers, the intra-manufacturing  
22 data was showing a broad variety of behavior. And

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1 the question then arises, well, how do you approach  
2 a project like that?  
3 Well, you start with the molecular  
4 structure, of course, and then you build on that  
5 and look at the structure of whatever the condensed  
6 phase is you're working with, and extract whatever  
7 knowledge that you can from that, and then proceed.  
8 So if we look at the existing literature at  
9 the time -- actually, before the time -- Steve  
10 Byrn's book, which is sort of a seminal reference,  
11 of course, had pointed out that if you had  
12 compounds that were hydrated, and levothyroxine is  
13 a pentahydrate, that desolvation could precede  
14 oxidative degradation. So that was known. So I  
15 would have hoped that we would have found that.  
16 We had published work classifying the  
17 hydrates, the structural basis of hydration in  
18 crystal structures. And we found that there were  
19 categories, such as channel hydrates, that would  
20 allow the egress and ingress of water, not at will  
21 but relatively facilely, depending on the  
22 structure.

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1 If you look at the structure -- I don't know  
2 how well you can see this in the light, but -- so  
3 this is the chemical -- the crystal structure, I  
4 should say. The chemical structure's on your  
5 right. The crystal structure shows that this is in  
6 fact a channel hydrate, so it can pick up and lose  
7 water.  
8 What we also found was that depending on the  
9 conditions of dehydration -- there's one of the  
10 students from LIU is working on the continuation of  
11 this project in the audience actually -- if you  
12 dehydrate this under certain conditions, the  
13 packing motif, that is, the way the molecules pack  
14 in the crystal structure don't change, so that  
15 leaves the pathway open, essentially, for small  
16 molecules, particularly gases, to infiltrate the  
17 crystal structure.  
18 So what you see here is from a publication.  
19 And you can see on the left-hand side that in fact,  
20 when you don't dehydrate, when you maintain it,  
21 fine. You take a crystal and put it on the bench,  
22 it's fine. And that's what the curves on the upper

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1 part of the loss profile show there. If you  
2 dehydrate it, even if you keep it at a relatively  
3 low temperature, it degrades.  
4 The graph on the lower right does the same  
5 sort of a treatment, but now this is with and  
6 without oxygen. So what Steve's book said about  
7 channel hydrates being able to dehydrate and  
8 oxidatively degrade is here. It was known.  
9 So we knew it was an NTI. It was known that  
10 it was a very low dose, so that the probability of  
11 getting -- even at the same level of degradation,  
12 could be a much larger percentage.  
13 It's chemically labile. That was also in  
14 the literature. There's a nice thesis from Patel  
15 from Cincinnati. You may know that. And  
16 processing affected the crystal structure because  
17 if you break this up and you dehydrate it, then  
18 it's labile. And there are excipient interactions  
19 known.  
20 Couple that with the fact that the half-life  
21 is 7 days. By the time you titrate your patient,  
22 as the doctors at the ACPS used to talk about, it

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1 could be months before you get to the point where  
2 you're stable. Now, go from one generic to  
3 another, or from brand to generic or vice versa,  
4 and there you have the length of time we're talking  
5 about.  
6 So what to teach? The dosage form specs  
7 need to be developed early. So you should design  
8 your dosage form to meet your specifications, not  
9 take the specifications that your dosage form gives  
10 you once it's made. I know that sounds illogical,  
11 but there you go.  
12 So the development process has to be  
13 integrated so you can predict the downstream  
14 effects. And we'll skip the rest of this, but  
15 suffice to say that orthogonal analytics are  
16 critical.  
17 So you really have to have a development  
18 based on categories. The data mining and creation  
19 of an NTI quality clinical response that is the  
20 same as a quality classification can be part of  
21 what we're talking about as a knowledge base and  
22 knowledge management. I won't go through it, but

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1 this is an example of the start of this sort of a  
2 process.  
3 So the research on integrated product  
4 development by category across disciplines is  
5 really critical, the example I showed you as well.  
6 The support for knowledge base R&D, for formulation  
7 design, has to be included like NIH includes the  
8 necessity of biostatistics in every application.  
9 And finally, development of programs for training  
10 and expert support for generic companies and  
11 reviewers is a key part of the proposals.  
12 So with that, I'll -- well maybe I won't  
13 end. No, that's the last slide, and I'll be glad  
14 to entertain questions.  
15 DR. LIONBERGER: Thanks much.  
16 DR. UHL: So again, back to this knowledge  
17 management, knowledge base, because I'm still  
18 having a hard time wrapping my head around this.  
19 So when I look at your third slide where you  
20 explain development history, and the development  
21 history basically creates the electronic living  
22 document. Right? So the development history would

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1 be the development history that the agency gets in  
2 an application from industry?  
3 DR. MORRIS: That's what I'd like to see. I  
4 think historically, development histories were not  
5 reviewed. And I'm not saying that it has to  
6 be -- that's something that's up to you -- but to  
7 me it makes perfect sense, yes.  
8 DR. UHL: Okay. I'm just making sure I  
9 understand where the data come from.  
10 DR. MORRIS: Yes, yes. Yes. From the  
11 development project.  
12 DR. UHL: So in that case, the data would be  
13 proprietary to the applicant. Correct?  
14 DR. MORRIS: Correct. Yes.  
15 DR. UHL: So can you walk me through, then,  
16 how this becomes something that's publicly  
17 available? Intellectually, I understand, or  
18 conceptually it can massively increase or improve  
19 product development. But how do we translate  
20 proprietary data into a kind of pre-competitive  
21 public/private partnership type thing?  
22 I'm looking at Ruth who deals in this space

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1 all the time. But it's yours and NIPTE's proposal,  
2 so I'd like to hear how you guys have thought  
3 through this because, as you said, the development  
4 history is in the application, therefore, it is  
5 proprietary. How do we make this a teachable  
6 database?  
7 DR. MORRIS: Right. No, no, that's a great  
8 question. And there's actually two, or depending  
9 on what group we're talking within NIPTE, three  
10 approaches.  
11 One is that the development history training  
12 is not just -- and I don't mean training in the  
13 mundane sense of the word, but I mean the  
14 introduction of the concepts that underlie the  
15 science that lead to the decisions that are made  
16 and the development history is part of it.  
17 So they're training, and it can take the  
18 guise, as we did with the PAT guidance under Ajaz's  
19 direction, where we would come and work with  
20 reviewers and go through the scientific part of it  
21 in enough detail so that it shows the integrated  
22 nature of the work.

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1 The second part, though, is that even though  
2 you can't -- it's sort of like when I was in  
3 industry. My research, my published research, was  
4 always one level more fundamental than the actual  
5 drug I was working on. Otherwise, they wouldn't  
6 let me publish it. And the way I look at it is we  
7 do that.  
8 In other words, we take that scientific  
9 basis and we take some specific examples, and maybe  
10 some of the more complex ones, as Steve said,  
11 because this is just an example. This one happens  
12 to be an oral dosage form, but it's the same for  
13 any dosage form.  
14 So you take these examples and then distill  
15 from them this approach that is based on the  
16 categories because if you look at part of the  
17 problems with the 14 dissolution specifications,  
18 for example, part of that is because we're trying  
19 to fit too many things into the same category. So  
20 there's going to have to be more granularity.  
21 Then that gets committed not just to  
22 training one-on-one, but gets committed to the

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1 database. PharmaHUB is, and the hub system in  
2 general -- the one at Purdue, at least, was -- it's  
3 all NSF-funded, I guess, and therefore it's public.  
4 It's secure.  
5 We can have a section of that that is  
6 password restricted to FDA accessibility, for  
7 example. But then the distilled part of that, the  
8 categorical treatment of the individual types of  
9 dosage, or of APIs and dosage forms, can be  
10 included for public dissemination. So that's the  
11 sort of two or three layers that we're talking  
12 about.  
13 Right now, if you go to pharmaHUB, and I  
14 don't have the link on my slide but I'll include it  
15 and send it so it can be put up on the web, you can  
16 take a course in crystallography. I mean, you can  
17 just start clicking and you can learn -- and, now,  
18 when I say crystallography, I don't mean  
19 crystallography like what's sodium chloride. I  
20 mean, Dave Morrighder [ph], who is one of our  
21 post-docs, developed molecular crystallography for  
22 drug substances. So it's very specific, so you

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1 don't have to go through three years of mathematics  
2 to be able to understand it.  
3 In this, I would see something much more  
4 akin to a searchable, like the FDA, website where  
5 you can put in a compound and find out what  
6 category it fits in if it's existing, particularly  
7 for generics. But you can also do it by category.  
8 You should be able to search by structure, and then  
9 dosage form types.  
10 So that's about as far as we've gotten. So  
11 I'm not saying we have the answers, but that's the  
12 idea. So it's really interactive. And in there,  
13 in the pharmaHUB too, the third tier is that we did  
14 ontological modeling. When I say "we," I mean the  
15 engineers did it and I helped them with the subject  
16 matter.  
17 So there's actually a database -- sorry,  
18 there's actually a program. I can't remember  
19 what -- it's an unfortunate acronym. It's POPE,  
20 but no offense was intended -- which is the Purdue  
21 ontology system to be able to say, okay, for an  
22 immediate-release, solid, oral dosage form, here's

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1 the decision tree and the ontology that leads you  
2 to a good formulation. It'll be a higher hurdle  
3 for the more complex dosage forms, but certainly  
4 doable. Sorry.  
5 DR. UHL: All right. Thank you. I would  
6 just say -- as an FDA employee, I can say this -- I  
7 hope whenever this becomes something, that is more  
8 or better searchable than the FDA website.  
9 DR. MORRIS: Yes. Well, I didn't want to  
10 put too fine a point on it, but yes.  
11 DR. LIONBERGER: Thanks very much, Ken.  
12 DR. MORRIS: Thank you.  
13 DR. LIONBERGER: So our next speaker is Eric  
14 Munson from University of Kentucky, also  
15 representing NIPTE.  
16 Presentation -- Eric Munson  
17 DR. MUNSON: So I want to thank the FDA for  
18 giving me the opportunity to talk with you about  
19 analytical characterization. You've already had a  
20 few lead-ins from the three speakers before as  
21 well.  
22 So I do have to put up a disclosure. I

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1 actually am partial owner of a company that  
2 provides services to the pharmaceutical industry,  
3 but I'm not going to be talking about any of that  
4 at this time.  
5 So what I remember from last year's GDUFA  
6 meeting was -- I believe it was Dr. Lionberger who  
7 actually said this, and I think he repeated it  
8 again today, so that supports that -- is that the  
9 only difference between an innovative product and  
10 the generic formulation, or generic product, is the  
11 formulation. So that really stuck in my mind.  
12 One of the things I decided to do is to  
13 figure out, how can we take that aspect and really  
14 use analytical characterization as a way of  
15 improving not only the product  
16 performance -- because that's one of the things  
17 that clearly has been an emphasis, looking at  
18 things like the in vitro composition, the  
19 dissolution properties and bioequivalence -- but  
20 then getting back and analyzing the product.  
21 The challenge has always been that analyzing  
22 the product has oftentimes meant analyzing maybe

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1 the ingredients, certainly the drug's excipients,  
2 but also, then, are there ways in which we can look  
3 at the processes? What happens during the process  
4 that maybe changes an excipient? And I'll get into  
5 that in a little bit greater detail here.  
6 So the idea is to actually translate what  
7 you learn from a formulation standpoint. So you  
8 have all these ingredients. You figure out not  
9 only see what are the drug substances that are  
10 there, but also then looking at the excipients,  
11 variability that exists, and then look at the drug  
12 product in much greater detail than what we  
13 currently do right now.  
14 But probably more importantly, try to  
15 understand what interactions occur between the drug  
16 substance and excipients in the drug product, and  
17 see what impacts those have upon the physical  
18 properties.  
19 So certainly, for example, we look at  
20 polymorphism in the drug substance, but it's  
21 actually quite rare that we spend a lot of time  
22 looking at polymorphism in the drug product. Also

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1 try and understand physical and chemical stability  
2 aspects.  
3 So in other words, what's the propensity for  
4 a drug to degrade once it gets into a formulation,  
5 which was actually one of the bases for one of our  
6 NIPTE projects on looking at the stability of  
7 gabapentin. And we were actually able to predict  
8 some of the stability properties based upon how the  
9 material was changed during processing.  
10 Fundamentally, once again, what we wanted to  
11 be able to do is to take the information that we'd  
12 learned on the drug substance and the drug product  
13 and translate that into a functional property, once  
14 again disintegration, dissolution, and the  
15 bioequivalence.  
16 So what I'm going to focus on for the rest  
17 of the talk is simply excipient variability. And  
18 that just so happens to be one of the topics I'm  
19 going to focus on, but that being said, there's a  
20 whole range of different ways in which we can look  
21 at drug product.  
22 So this came from a presentation that was

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1 given by someone from the FDA, where essentially  
2 risk reduction opportunities, there were two very  
3 common causes that were listed. One is deficient  
4 facilities and processes, and essentially that came  
5 down to humans, and then ingredient variability, so  
6 with excipients.  
7 So this is certainly something that will be  
8 addressed in a few other talks later today. I know  
9 certainly that an organization like IPEC is  
10 interested in excipient variability, or the lack of  
11 excipient variability, and trying to show whether  
12 excipients are equivalent. But certainly there  
13 have been recalls due to excipient variability.  
14 A lot of these happen to be due to things  
15 like codeine, but fundamentally, what they amount  
16 to is that you end up with a failed dissolution  
17 specification because an excipient may have been  
18 changed to a different vendor. Even the natural  
19 variation that comes based upon the time at which a  
20 natural excipient was harvested can potentially  
21 have an impact.  
22 So I want to highlight one particular case.

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1 If you're not familiar with magnesium stearate, you  
2 probably should be. It's one of the most commonly  
3 used excipients used in oral dosage forms. It's  
4 also a very complicated excipient, naturally  
5 derived.  
6 Even though it's called magnesium stearate,  
7 in order to be called magnesium stearate it just  
8 has to be 40 percent stearate by composition and 90  
9 percent stearate and palmitate. And then you can  
10 have any sort of range of other fatty acids that  
11 can exist.  
12 What's shown here on the left is the solid-  
13 state NMR spectrum of three different magnesium  
14 stearate samples that we obtained. And this is  
15 showing the carbonyl region. And essentially, what  
16 I want to highlight here is the fact that when  
17 you're looking at this, there are quite large  
18 variations.  
19 The top one represents a disordered form of  
20 magnesium stearate. The middle one represents a  
21 mixture of, actually, a monohydrate and a dihydrate  
22 form of magnesium stearate. And then the bottom

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1 one represents a monohydrate form. And then you  
2 have the corresponding differential scan  
3 calorimetry data up on the top, and then the  
4 corresponding thermographic metric analysis.  
5 A couple of points is that if you look at,  
6 for example, the top one there, it has a very  
7 different DSC thermogram. So this the top one.  
8 And maybe I'll show over here. You can see the top  
9 one there has a very different DSC thermogram than  
10 does the third one.  
11 Yet if you look at the water contents,  
12 they're essentially -- the amount of water that's  
13 lost is basically the same. They come off with  
14 different points in the TGA, but they are very  
15 different. So the question is -- we can certainly  
16 see that there are differences.  
17 One of the challenges that you have when  
18 you're dealing with magnesium stearate is how to  
19 actually characterize it inside of a formulation.  
20 And the challenge is that the bottom here  
21 represents just an NMR spectrum of magnesium  
22 stearate, and the area that's shown here in the box

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1 on the left, you can see that that represents  
2 magnesium stearate in this particular form, which  
3 is very crystalline.  
4 But when you put it into a formulation, it's  
5 practically impossible to see that. So how do you  
6 see a material that's present at 1 percent of  
7 formulation, and especially study it  
8 scientifically?  
9 Our approach has been to actually make our  
10 own magnesium stearate. What we do is we C13 label  
11 it. And the advantage of C13 labeling is that a  
12 signal that was present at only 1 percent by  
13 natural abundance now is present at 100 percent.  
14 So it's very easy for us to actually identify the  
15 form of magnesium stearate that's present in this  
16 sample.  
17 This is one of our very first attempts,  
18 where we started off with a mixture of a  
19 trihydrate, a monohydrate, and a dihydrate. And  
20 what we see is that as the material is blended, the  
21 trihydrate basically disappears, is converted to  
22 monohydrate. The dihydrate also disappears as

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1 well.  
2 So there's definitely form changes that  
3 occur in the magnesium stearate as you do the  
4 blending process. So we can use this as an  
5 analytical technique to start to really  
6 fundamentally understand what happens to magnesium  
7 stearate inside of a formulation.  
8 Now the issue is, of course, does this  
9 really matter? So the other thing that we're  
10 working on in the laboratory is trying to do the  
11 correlation of the dissolution data back to what we  
12 can identify as the change in the NMR.  
13 You can just see here simply very similar  
14 changes, or you can see that magnesium stearate,  
15 depending upon how it's mixed -- this is hand  
16 mixing so it's quite variable -- but you can see  
17 that it does have a pretty significant impact upon  
18 the dissolution.  
19 One of the things that we did is then we  
20 actually tried to do very consistent, relatively  
21 mild mixing. And you can definitely see here the  
22 difference between the monohydrate form and the

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1 trihydrate, the net result being that there are  
2 considerable differences in terms of -- well, there  
3 are differences between the monohydrate and the  
4 dihydrate in terms of how it impacts the solution.  
5 And we've done this for a number of different  
6 cases, looking in this particular case that the  
7 trihydrate always comes out last.  
8 Interestingly, the disordered form, which is  
9 one of the things that we would have thought would  
10 have been coating the particles the most, actually  
11 didn't seem to do that. And that was quite strange  
12 for us. But trying to understand the nature of, as  
13 you go from one magnesium stearate source to  
14 another, which is something especially in the  
15 generic industry, could be a very big deal How do  
16 you deal with that? So we can see once again  
17 another example of the impact upon comparing the  
18 trihydrate versus the dihydrate and the  
19 monohydrate.  
20 So what I'd like to do is to summarize.  
21 What does this mean? So fundamentally, it comes  
22 down to characterizing not just the performance,

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1 and there's a lot of impact on the performance, but  
2 also the product. And I think that there is a lot  
3 of emphasis, and I've seen that a lot, in the  
4 presentations that have been given today. So what  
5 it really amounts to is doing that advanced  
6 analytical characterization of dosage forms using  
7 the variety of analytical techniques that are  
8 available to you.  
9 The concept is really to understand the  
10 complex dosage form, so really understand not just  
11 what went into it, but after it's made, how is it  
12 put together. And then convert this into a  
13 knowledge base that's accessible. So, for example,  
14 we talk about the excipients database, which  
15 contains either the quantities of excipients, but  
16 doesn't really address things like excipient  
17 variability.  
18 Then the third thing is to translate that  
19 through to reviewers through an education process.  
20 And please, please, ask me about the education  
21 process because I would like to provide a little  
22 bit more detail as well on that.

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1 Fundamentally, you can see at the bottom,  
2 what do we want to have the FDA get out of this?  
3 And what we really need to do is to say, okay, when  
4 you have an analytical approach, what are the  
5 different techniques that we'll give you to be able  
6 to tell you what do you have inside of a product?  
7 Then how do you integrate this into that  
8 design development space? And then how do you  
9 validate it? So in other words, especially when  
10 you come up with some of these newer methods, how  
11 are you able to validate them?  
12 Another question is that how well do these  
13 work across the dosage forms? So certainly we saw  
14 a lot of different dosage forms that potentially,  
15 for example, could be characterized using solid-  
16 state NMR spectroscopy. A lot of the ones that  
17 were presented in the first talk of today could  
18 certainly be studied that way.  
19 Then fundamentally, when you have this  
20 information, how do you translate that into QC  
21 testing. Okay? And then when you have a root  
22 cause investigation associated with something that

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1 fails, how do you take these approaches and be able  
2 to solve your problem?  
3 With that, I'll be happy to answer any  
4 questions you have.  
5 DR. LIONBERGER: Thanks much.  
6 DR. BUHSE: So you and several before talked  
7 about education of reviewers. But it also seems  
8 that there needs to be maybe, potentially, a  
9 fundamental education of drug developers as well in  
10 terms of if they develop it, or if they ask the  
11 right questions up front, before they start,  
12 even --  
13 DR. MUNSON: Yes.  
14 DR. BUHSE: -- potentially, then we're not  
15 put in a position where we have to try to figure  
16 out that they used the wrong mix, data area, or  
17 whatever. So it seems like the education needs to  
18 start pretty far back in the chain, even before we  
19 see a drug.  
20 Is there a way you can infiltrate your  
21 knowledge, et cetera, to especially the generic  
22 industry, a lot of which often are not located in



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

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

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

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

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1 industry do care about. And that is one of the  
2 things that we're trying to address.  
3 Now, once again, I can't speak for the  
4 generic industry per se. But I think that these  
5 are topics that they care about. And certainly  
6 education, I think, is something that they would  
7 also be very interested in, especially because if  
8 anything, that helps them get through the review  
9 process, so that the FDA people and the people in  
10 the generic industry understand that they're  
11 getting the same level of education, that that  
12 would actually be quite beneficial for them going  
13 through the review process.  
14 DR. LIONBERGER: All right. Thanks very  
15 much, Ken.  
16 So we'll move on to our next speaker. It's  
17 Professor Amy Barton Pai from the Albany College of  
18 Pharmacy and Health Science.  
19 Presentation – Amy Barton Pai  
20 DR. BARTON PAI: Good afternoon. I just  
21 wanted to extend my thanks to the FDA OGD for  
22 giving me this opportunity to really talk to you

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1 about challenges relevant to bioequivalence  
2 assessment with IV iron formulations.  
3 My research program focuses on differential  
4 toxicity profiles of IV iron formulations, but in  
5 addition, I am a nephrology-trained clinical  
6 pharmacist, and I've worked in the dialysis  
7 population for more than 20 years. And this  
8 population is a ubiquitous user of these agents, so  
9 it is a very relevant topic.  
10 I have nothing to disclose.  
11 As Dr. Lionberger really teed up nicely in  
12 his opening remarks, IV iron formulations are  
13 complex products in that they are colloidal  
14 suspensions of nanoparticles. This is something  
15 that I don't think most clinicians who use these  
16 products appreciate, so they do have unique  
17 challenges.  
18 Most of our experience with these products  
19 is actually gleaned from the global market, where  
20 there are many generic iron sucrose products  
21 available globally. The regulatory oversight for  
22 these products is variable. And typically,

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1 countries that utilize these generics have mandated  
2 switches.  
3 What we do know is that some animal models  
4 have pretty universally shown increased oxidative  
5 stress induction and higher tissue deposition of  
6 iron with generic formulations of iron sucrose  
7 compared the reference listed products.  
8 Clinical observational studies are also  
9 accumulating in the literature as these mandated  
10 switches have occurred. And they have demonstrated  
11 reduced efficacy as well as increased adverse event  
12 profiles related to the generic products versus the  
13 RLDs. Notably, these differential safety and  
14 adverse event profiles have been mechanistically  
15 linked to direct release of labile iron from these  
16 formulations.  
17 So through some UO1 funding, our group was  
18 able to really engage in a systematic approach to  
19 try to better predict serum non-transferring-bound  
20 iron, which is also known as labile iron, from IV  
21 iron formulations.  
22 Our project essentially looked in tandem at

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1 studying a multiplicity of different assays to  
2 measure labile iron through chelatable and redox  
3 active mechanisms. We then studied all of these  
4 assays in vitro to determine possible applicability  
5 for measurement in vitro, and then subsequently  
6 chose candidate assays to measure labile iron  
7 release in vivo.  
8 The products we studied were all of the  
9 currently available reference listed drugs at the  
10 time this study was initiated, as well as the only  
11 approved US generic, which is sodium ferric  
12 gluconate complex.  
13 After the data from the in vitro and in vivo  
14 pieces were accumulated, we sought to see if some  
15 of these data could at least potentially begin to  
16 inform an in vitro to in vivo correlation model.  
17 So I'll walk you through a little bit of this  
18 project.  
19 Essentially, at the very beginning, we  
20 exposed all of the products to the typical battery  
21 of physical-chemical characterization techniques  
22 that are used in the nanoparticle space. The ideal

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

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

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

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

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1 So we essentially are not able to compare these  
2 compounds.

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

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

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

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

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

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

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

22 So moving on, this is our in vivo

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

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

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

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

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1 carbohydrate complex. So what you can see in this  
2 analysis relevant to the RLD and generic is that  
3 this KR is very similar between the two drugs.  
4 So wrapping up here with what I believe is  
5 probably still needed in this arena, clearly we  
6 need further evaluation of physical-chemical  
7 characterization limitations for inter-product  
8 comparison. This could even be as granular as  
9 instrumentation that's used between manufacturers.  
10 We certainly need to study additional  
11 formulations, both in vitro and in vivo. Again,  
12 this represented just a single generic IV iron  
13 formulation. So many more need to be studied,  
14 whether that's in the global marketplace or handled  
15 domestically.  
16 Lot-to-lot variations is another issue that  
17 has presented itself on the global market, with  
18 differences in labile iron release between lots.  
19 It will be important to more clearly define the  
20 optimal assay for labile iron measurement, both  
21 in vitro and in vivo. And essentially, leading to  
22 further analyses, to possibly develop stronger and

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1 more predictive models for labile iron release that  
2 obviate the need for in vivo work.  
3 Finally, as these products start to emerge  
4 on the marketplace, as a clinician I believe it's  
5 really important to have close marketing  
6 surveillance of these products, as well as  
7 assessing usage patterns.  
8 Ultimately, working in this space for the  
9 past 20 years, I can say that clinicians who use IV  
10 iron products are not aware of the complexity of  
11 these formulations, and should be educated on the  
12 complexity and the unique challenges that exist.  
13 With that, I'll conclude, and I'm happy to  
14 take any questions.  
15 DR. LIONBERGER: So with respect to your  
16 comment on -- there's multiple currently approved  
17 products. Do clinicians think that they are  
18 different, or do they interchange them? You know,  
19 is there a sense that there are differences between  
20 the approved different RLDs or not?  
21 DR. BARTON PAI: I would say the clinician  
22 perceives the dominant differences as

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1 immunogenicity, and their ability to give a larger  
2 dose in a single infusion. But as far as physical-  
3 chemical characteristics, they, I would say, are  
4 largely unaware. They dose iron. It's all based  
5 on elemental iron, so their switching is based on  
6 safety profiles as well as ease of administration  
7 when giving larger doses in more outpatient  
8 settings.  
9 DR. CONNER: The one generic that you had in  
10 your list, what was the RLD for that, the reference  
11 listed drug?  
12 DR. BARTON PAI: Ferrlecit.  
13 DR. CONNER: Ferrlecit. So the real  
14 comparison, or test of your methods, is comparing  
15 that generic to Ferrlecit?  
16 DR. BARTON PAI: That's right.  
17 DR. CONNER: How well does that do in your  
18 testing?  
19 DR. BARTON PAI: So again, just to recap the  
20 data here, in many of the physical-chemical  
21 characterization pieces, there were differences  
22 between the RLD and the generic, possibly because

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1 of, again different steps in the analytic process.  
2 The in vitro piece, it looked like the brand had  
3 more labile iron release. However, in vivo, again  
4 those profiles were very similar.  
5 DR. UHL: Could you go back one slide? Same  
6 question I asked earlier this morning. So you've  
7 got seven potential ideas. We have about  
8 \$20 million on an annual basis. So could you tell  
9 me what your number one priority would be,  
10 especially as it relates to this aspect of IV iron  
11 therapy?  
12 DR. BARTON PAI: I think this ties in  
13 certainly to the confidence in substitution. So in  
14 an incremental way, I would say the predominant  
15 piece is elucidating these physical-chemical  
16 characterization limitations because that's  
17 inherent in the guidance right now, and following  
18 up with additional in vitro and in vivo study of  
19 additional generic formulations.  
20 DR. LIONBERGER: Thanks very much.  
21 So our next speaker is Professor Diane  
22 Burgess from the University of Connecticut.

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1 Presentation – Diane Burgess  
2 DR. BURGESS: Got to be able to walk fast  
3 here. Okay, good afternoon. Thank you for the  
4 invitation. I'm very pleased to be here. Probably  
5 need my glasses to work out how to figure this.  
6 So what we've been doing in one of the  
7 grants that we have is with microspheres. I'm  
8 presenting that work because it's furthest along.  
9 We've been developing Q1/Q2 microsphere  
10 formulations that we're deliberately doing with  
11 minor manufacturing changes, very minor, to see  
12 what are the critical manufacturing changes that  
13 can have an effect on the product performance.  
14 So we chose, first of all, Risperdal Consta,  
15 but we are working on other drugs as well. So we  
16 chose Risperdal Consta and we made very small  
17 changes with, as you can see here, the -- so we  
18 used different solvents, a DSM and ethyl acetate.  
19 And we also made other slight changes in the method  
20 of mixing and the method of sieving.  
21 So we had drug loading very similar. And  
22 this slide had some of the physical-chemical

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1 characteristics -- the particle size, not too much  
2 differences in particle size, a little bit with the  
3 difference in the sieving and with the difference  
4 in the mixing here.  
5 But what I really want to point out here is  
6 the difference in the porosity because with the  
7 ethyl acetate, we got much more porous microspheres  
8 compared to with the DCM. This was also more  
9 similar to the reference listed drug product.  
10 So in moving on, we did our in vitro release  
11 testing. And the typically used method is a sample  
12 and separate method for microspheres, as reported  
13 in the literature. But in our lab, we've developed  
14 another method several years back, which is an  
15 apparatus 4, where we put the microspheres between  
16 the glass beads and hold them in the apparatus 4  
17 flow-through cell. The advantage of this method is  
18 you get around aggregation problems as well as  
19 floating problems that can happen with the sample  
20 and separate and even USP 2 apparatus.  
21 This is results with the sample and  
22 separate. And we found that we did have some

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1 aggregation, and we were able to resolve some of  
2 that by using surfactant for the sample and  
3 separate method. So we were able to get a better  
4 resolution of our four different microsphere  
5 products. This is not with the RLD, but the four  
6 that we were making Q1/Q2.  
7 With the apparatus 4, we got -- again, very  
8 good differences here were able to show up. And  
9 one thing I wanted to point out is that with the  
10 more porous microspheres, the two that were made  
11 with ethyl acetate, with either method we didn't  
12 see very much burst release.  
13 That method of manufacturing had eliminated  
14 some of the burst release, whereas with the other  
15 method, where it was less porous, we were getting  
16 burst release. So that was one significant  
17 difference, as well as the slight differences in  
18 the rates that we can see here.  
19 We then went on to do in vivo work that we  
20 did in rabbits. So this is an IVIVC, as such, with  
21 rabbit data. And we used the Loo-Riegelman method  
22 to deconvolute the data. So this on the top here

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1 is our rabbit data. So our in vivo release profile  
2 with a rabbit for Risperdal Consta, this is the  
3 RLD, and here we have the deconvoluted.  
4 I'm showing the RLD here because we can,  
5 from the literature, get the human data from the  
6 literature -- for the RLD, obviously not for the  
7 formulations we made. And we can see here we've  
8 deconvoluted this data so there is very good  
9 similarities but inter-species difference, as  
10 you'll probably notice here, much, much faster in  
11 the rabbit.  
12 In our rabbit model, we used the hind leg,  
13 whereas the human it's into the gluteus maximus.  
14 Big differences in fat content and also in the  
15 vascularization. Vascularization is probably the  
16 bigger difference, where you're going to get more  
17 ready dissolution, larger volume there. And the  
18 other difference is, of course, is the metabolism  
19 in the rabbits. We did do the risperidone. We  
20 looked at risperidone in vivo, and there are  
21 differences in the metabolism.  
22 So looking at the four formulations that we

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1 made, the big difference here is the two with the  
2 burst release. That's obviously going to be your  
3 Cmax and Tmax, whereas the ones without the burst  
4 release, their Cmax and Tmax is -- so is shifted,  
5 obviously. So that was one big difference here.  
6 But we went on to do our deconvolution. And  
7 our four formulations are to the left, and the  
8 Risperdal is the red one to the right. So what we  
9 did is we used three of our formulations to make an  
10 IVIVC in order to predict the fourth formulation,  
11 so 1, 2 and 3 to predict 4, or 2, 3, 4 to predict  
12 1, and so on. So this is our IVIVC for 4/3  
13 combinations.  
14 Then we used this to predict the in vivo  
15 release for the fourth one, and you see here we're  
16 getting really very, very good prediction. So this  
17 is for a complex product. Microsphere is one of  
18 the most complex, especially when you've got the  
19 three phases of the burst, the lag phase and then  
20 the secondary release profile. So we were very  
21 pleased with this.  
22 We also used these four to predict the RLD.

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1 And again, you'll see really, really good  
2 prediction. And based on the USP 4 apparatus  
3 method, we got really excellent prediction, the PE  
4 of 10 percent or less. When we did use the sample  
5 and separate method, which we had shown wasn't as  
6 good an in vitro release method, at least for these  
7 microspheres, then we didn't get a good IVIVC. It  
8 was basically inconclusive at best.  
9 So we're now working, or we've just  
10 completed a study also with naltrexone. And this  
11 is two-phase. This doesn't really have burst  
12 release, but we've got three formulations. And  
13 we've shown excellent, again, IVIVC for these three  
14 formulations for the naltrexone as well. And we're  
15 now working on a peptide formulation.  
16 So I think that, to quote from Ajaz, that I  
17 think we're moving from the microspheres, from just  
18 being a complex dosage form, to a complicated one,  
19 if I understood what Ajaz was saying correctly;  
20 that now we're really starting to understand the  
21 physical-chemical properties that are important,  
22 and we are able to develop an IVIVC so we could be

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1 able to -- in the future, obviously with more  
2 information and really, really good physical-  
3 chemical characterization, we could be able to move  
4 towards at least some looking at bioequivalence for  
5 this type of product.  
6 Another product that I think we haven't  
7 worked on yet but I think we should is the  
8 long-acting suspensions because I think this is a  
9 kind of low-hanging fruit, relatively easier  
10 formulation, from the formulation and manufacturing  
11 perspective. So I think this would be a good one  
12 to tackle next.  
13 The one that Chetan mentioned, the  
14 ophthalmic, we are doing some work on the  
15 ophthalmic area. And there I think we can get a  
16 very good in vitro release method, definitely, that  
17 could discriminate between manufacturing  
18 differences. But to move towards an IVIVC for  
19 something like ophthalmic, I think, would be, as  
20 Chetan pointed out, very difficult. So some of the  
21 physical-chemical characteristics might be more  
22 important or at least as important there.

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1 The last thing I wanted to say was talk  
2 about the in vitro and in vivo stability issues  
3 with these complex products. With the  
4 microspheres, for example, I'm familiar, and some  
5 of the other PLG formulations. We get interaction  
6 with the drug such as risperidone and naltrexone.  
7 Even with the peptide drugs, we've got  
8 interactions. And with the peptides, it could be  
9 even more complicated because of the potential  
10 immunogenicity problem.  
11 These interactions can occur during  
12 manufacturing; with different manufacturing,  
13 methods may get more or less of the interactions  
14 with these drugs, so more or less possibility for  
15 immunogenicity, and so on. And how you manufacture  
16 them can also change how they may behave during  
17 shelf life storage because of different porosity  
18 and so on with the humidity conditions.  
19 That also can impact on those changes  
20 occurring in vivo when you're looking at some of  
21 these products, or not just weeks, but months and  
22 even years, in the body in that human environment

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1 with porosity and so on. So I think that this is  
2 another area that I think we need to have some  
3 focus on.  
4 So just to acknowledge the funding,  
5 particularly the FDA funding there in the middle.  
6 And my research group, and to the left of me is Jie  
7 Shen. She did a lot of the work I presented today.  
8 Also, Janki to the left of Jie. And then this is  
9 some of the rest of my group. So thank you.  
10 DR. LIONBERGER: Thank you. So one of the  
11 challenges in these products is that since they're  
12 long-acting, you have to do very long PK studies to  
13 show bioequivalence. So how far are we, or what  
14 new data would we need, potentially, to support a  
15 waiver of a bioequivalence study?  
16 DR. BURGESS: Well, I think with the  
17 microspheres, I can speak. I think we're getting  
18 very close to really understanding what are maybe  
19 the Q3 type of things, Something like the porosity  
20 would be a Q3 property, so to understand those  
21 properties.  
22 There are a few products that we could still

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1 do and attempt to do IVIVC. And we've been able to  
2 develop what I think are very robust IVIVCs for two  
3 products now.  
4 So I think that we're really moving in that  
5 direction because we're able to use those two, for  
6 example, to predict the RLD. And even with two of  
7 those having a burst release and two not having a  
8 burst release, we still got pretty good prediction.  
9 So I'm confident that we're moving in that  
10 direction. And with more robust -- if the generic  
11 companies do a very good physical-chemical analysis  
12 of their product, I think if they have a good  
13 portfolio with that I think we could be able to  
14 move forward with that for them.  
15 DR. LIONBERGER: All right. Thank you very  
16 much.  
17 DR. BURGESS: Thank you.  
18 DR. LIONBERGER: So our next speaker is  
19 David Gaugh, representing GPhA.  
20 Presentation - David Gaugh  
21 DR. GAUGH: Thank you, Rob, and good  
22 afternoon, panel. And thank you for holding this

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1 public meeting. We greatly appreciate it. As one  
2 of the key stakeholders in the GDUFA realm, if you  
3 will, this is very important and near and dear to  
4 our hearts of the generic industry. So thank you  
5 for holding this public meeting.  
6 I think at least the panel, I know, knows  
7 all about GPhA, so I'm not going to go through  
8 this. And I believe these are going to be made  
9 public, so the rest of the audience will be able to  
10 see them. But you can read them as we go along.  
11 Just a list of our members. So we represent  
12 approximately 35 full members and approximately  
13 45 associate members. So a large spectrum of the  
14 generic pharmaceutical industry is represented by  
15 GPhA.  
16 If you take not this slide and the numbers  
17 that are on the slide, over 90 percent of the  
18 products manufactured and sold for use in the  
19 United States is represented by the GPhA companies.  
20 So if you have questions about generics. we can get  
21 that message out pretty readily to most of the  
22 constituents.

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1 Statement of mission. I know that there  
2 isn't a specific mission statement that the  
3 regulatory science team has, but this is coming  
4 from an article and an interview that  
5 Dr. Lionberger had last year.  
6 We think it's very important to make safe  
7 and effective generic drugs available to the  
8 American public by ensuring that OGD standards, as  
9 reflected in review guidance and communication to  
10 sponsors and the public, continue to be based on  
11 the best currently available science and results of  
12 regulatory science research. So we think that's a  
13 very important tenet to keep at hand.  
14 If you look at the GDUFA goals letter, which  
15 was developed back in 2012, "FDA will convene a  
16 working group and consider suggestions from  
17 industry and other stakeholders to develop an  
18 annual list of regulatory science initiatives for  
19 review by CDER director."  
20 Again, we think very important. This public  
21 meeting is one of those opportunities for a working  
22 group, but as you'll see as I go through my slides,

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1 we think there's other opportunities for working  
2 groups and collaboration that we would like to see  
3 the agency take on going forward.  
4 GPhA and other stakeholders began dialogues  
5 with FDA to explore how best to broaden industry's  
6 input into the development process of the annual  
7 list. But to date, no action plans that we  
8 presented have been taken up, so we hope that these  
9 working groups will help us get to that point.  
10 While GPhA is supportive of the regulatory  
11 science initiative, payers into the GDUFA program  
12 want more input, and one public hearing is not what  
13 we consider to be enough. So therefore, we're  
14 asking for more working groups going forward.  
15 So what I'm going to do is not address  
16 specific products per se, but opportunities for  
17 input, if you will, and consideration. So  
18 increased collaboration to identify the annual  
19 regulatory science priorities. Increased  
20 transparency and involvement with the decision-  
21 making process for the user fees that are used.  
22 User fee funding of studies and projects to

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1 be distributed in terms of short, intermediate, and  
2 long-term goals so the generic industry can benefit  
3 from the knowledge gained from the results of these  
4 studies, projects, in real time as much as is  
5 possible. And again, we've already talked about  
6 the working groups.  
7 From a transparency standpoint, FDA to  
8 improve transparency and communication regarding  
9 how it determines the focus of the studies and  
10 projects, determines the scope of those studies and  
11 projects, and their benefit.  
12 Determines how the results of the studies  
13 and projects are interpreted and utilized by the  
14 FDA. And determines the overall impact of the  
15 science and regulatory initiative program that has  
16 had an increase in patient access to generic  
17 medicines.  
18 So there were some specific points that  
19 Dr. Lionberger and team put out for consideration,  
20 and so here are some suggestions that we think  
21 would be very important. And the user fee monies  
22 that are provided, we think, would benefit greatly

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1 from this as well.  
2 Opportunities for scientific or technical  
3 advancements: First, a discussion and expectations  
4 on nanotherapy and characterization. Opportunities  
5 to have scientific exchanges between industry and  
6 FDA in the form of workshops. I think I've said  
7 that a few times already.  
8 Number 2, innovative approaches to  
9 pre-approval development of generic drugs, so  
10 discussions and expectations on in vivo and  
11 in vitro correlation methods for low-dose  
12 concentration products such as otics, ophthalmics,  
13 long acting injectables, and auto injectors.  
14 Discussions and expectations on product  
15 subject to clinical endpoint studies in which the  
16 primary endpoint is difficult to measure and/or  
17 difficult to distinguish.  
18 Discussions around developing a premise with  
19 well-defined in vitro methodologies to replace the  
20 need for clinical endpoint studies is another  
21 consideration. Discuss and expectations on setting  
22 clinical relevant specifications. And discussions

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1 and expectations on qualifications of dissolution  
2 apparatus and methods.  
3 Third, innovation in scientific approaches  
4 to evaluating the therapeutic equivalence of  
5 generic drug products throughout their life cycle,  
6 so the narrow therapeutic index products and drug  
7 device combination products.  
8 Four, the high-impact public health issues  
9 involving generic drugs that can be addressed by  
10 prioritizing allocations for the fiscal year 2017  
11 funding. Timely guidance developed for high impact  
12 generic products, first generics, NCE-1 products,  
13 and very importantly, complex products.  
14 Number 5, identification of specific issues  
15 related to generic drug products or scientific  
16 recommendations and/or clarifications are needed.  
17 So discussions and expectations of long-acting  
18 microparticles of aseptic processing on  
19 characterization of peptides and iron products; on  
20 the characterization needed to show similarity for  
21 devices for combination products.  
22 The risk analysis for delaminating glass



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1 vials and potential testing specifications for this  
2 delamination. Extractables, leachables for all  
3 dosage forms, sterile and non-sterile.  
4 Expectations on generic abuse deterrent formulation  
5 products on a USP Chapter 232, Elemental  
6 Impurities.  
7 On adhesions for transdermal products, on  
8 guidance to address the limitations with current  
9 scoring scales and statistical methodology for  
10 assessing non-inferiority and adhesion and  
11 irritations for transdermal products.  
12 Finally, under number five is the evaluation  
13 of the approach to safety evaluation for certain  
14 types of commonly-used excipients.  
15 Number 6, strategies for enhancing quality  
16 and the equivalent risk management during generic  
17 drug product development. Assessment of the  
18 comprehensive safety risk for food additives in  
19 oral drug products.  
20 So additional points to consider besides the  
21 six that you provided to us and we tried to give  
22 you some clarity on response; those are not deep

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1 dives, as you can tell, but we would love to be  
2 able to, as you develop programs, get into those  
3 working groups that we talked about before.  
4 But one such area was the creation of new  
5 tools by the FDA for use in assessing the safety,  
6 effectiveness, quality, and performance of generic  
7 drug products. We think that's critically  
8 important, and I've heard that already two or three  
9 times today.  
10 The scope of this request was to include,  
11 but not limited to, the FDA addressing the concerns  
12 with regards to the reviewer consistency, updating,  
13 improving, and enhancing the IID, as well as  
14 improving the quality of the submissions that we're  
15 talking about.  
16 Industry's ask on the IID was to ensure data  
17 reliability and the ability of industry and FDA to  
18 make consistent and sound regulatory decisions,  
19 improving quality standards for drug development,  
20 and encouraging and promoting innovation.  
21 So in conclusion, we look forward to working  
22 closely with the FDA and other industry

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1 stakeholders, besides just the generic industry, in  
2 order to develop a comprehensive and meaningful  
3 2017 regulatory science initiative program.  
4 Thank you, and happy to take any questions.  
5 DR. LIONBERGER: Thank you, David.  
6 DR. BOAM: Thank you, David. I was just  
7 going to ask, and since I realize this is probably  
8 a compilation of recommendations from your members,  
9 would just welcome a follow-up to the docket. But  
10 one of the items under number 5 you asked for was  
11 discussion expectations on aseptic processing.  
12 It would be useful to know what about our  
13 current guidance on aseptic processing is lacking.  
14 If there are certain aspects of that you'd like us  
15 to expand upon, or if there's certain things that  
16 are either not covered or not covered clearly in  
17 that guidance, we would certainly welcome that  
18 input.  
19 DR. GAUGH: So no, we're going to start  
20 working groups on these ourselves. So whether  
21 they're taken up by the agency or not, we'll have  
22 working groups on them. So a lot of things have

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1 been changing over the past few years on aseptic  
2 processing, and we want to make sure that we have a  
3 clear understanding as the agency moves along the  
4 spectrum of what aseptic processing is acceptable  
5 and what is not. So we can come back with more  
6 details.  
7 DR. BUHSE: Thank you. These are many  
8 specific targeted recommendations. But I want to  
9 take a step back and ask about some of the terms  
10 you used. I understand that the members in GPhA  
11 are seeking more input into the development of the  
12 regulatory science initiative.  
13 When you make a request for a discussion and  
14 expectations, I think I understand the expectations  
15 point. But with respect to the discussion, are  
16 your members looking for an ability to speak with  
17 FDA as we develop these scientific understandings,  
18 or develop the scientific regulatory agenda to  
19 address those? Or are you referencing more  
20 discussion once we have developed these with  
21 individual companies in a one-on-one way or  
22 iterative way? Can you just talk a little bit more

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

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

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

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

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1 Ashley's -- about the aseptic. So we're looking at  
2 that as well.  
3 DR. LIONBERGER: We'd encourage, in topics  
4 where you have interest from multiple companies, to  
5 facilitate forming these groups and having those  
6 groups provide very specific recommendations into  
7 the docket. If they're prepared this year, get  
8 those groups to send in their consensus, things  
9 into the docket in particular areas.  
10 DR. GAUGH: Right. Absolutely we will.  
11 Yes.  
12 DR. STODART: Thank you. On slide 7, you  
13 mention several methods or several areas where we  
14 can improve transparency and communication. Do you  
15 have any specific suggestions as how we would go  
16 about achieving that?  
17 DR. GAUGH: I'm sorry. You said slide 7?  
18 DR. STODART: Slide 7, for transparency and  
19 communication.  
20 DR. GAUGH: I'm still having a hard time  
21 hearing which one --  
22 DR. STODART: No. On slide 7, you list

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1 about five different areas in which FDA can improve  
2 its transparency and communication. So I was just  
3 asking whether there are any specific suggestions  
4 you have as how we could go about achieving that.  
5 DR. GAUGH: Again, no. We've just started  
6 the working groups. So in the past years, to Rob's  
7 point, we haven't had these robust working groups  
8 together yet, and so we've just started pulling  
9 those together. After conversations that we've had  
10 with GDUFA negotiations in the past many months, we  
11 realize to get to that point that you're asking  
12 about, we need to get these working groups  
13 together.  
14 DR. STODART: Thank you.  
15 DR. GAUGH: You're welcome.  
16 DR. CONNER: Yes. There are quite a few  
17 points here where you're obviously asking for more  
18 input into the regulatory program. But to repeat  
19 Cook, who has made this -- and I'll make the  
20 request before I make my comment, that you have a  
21 rather large list of good ideas here. But only  
22 being approximately \$20 million, do you have any

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1 prioritization or do your members have any  
2 prioritization?  
3 It folds into the next question. Obviously,  
4 even if you look at the list of members you have  
5 here, not to mention the other non-GPhA  
6 constituents of the generic drugs program, which  
7 often have very different interests, how would you,  
8 or we, prioritize these things when you have so  
9 many constituents of your own with very different  
10 priorities and very different opinions about what's  
11 important and what's not?  
12 DR. GAUGH: You ask a great herding-the-cats  
13 question.  
14 DR. CONNER: Right.  
15 DR. GAUGH: So to answer your question, we  
16 do have a large regulatory working group, and we  
17 will go through now and work on this and get those  
18 priorities there. You're right, there's \$20  
19 million that was earmarked out of GDUFA I, but I  
20 don't think that necessarily stops the agency from  
21 using more than \$20 million in the GDUFA dollars or  
22 in appropriation dollars.

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1 So we think there's opportunity for an even  
2 broader base of projects and programs to work on.  
3 But to your point, we'll come back with a priority  
4 list because we know you can't work on all of these  
5 that we're listing out, absolutely.  
6 DR. LIONBERGER: All right. Thank you very  
7 much, David.  
8 DR. GAUGH: Thank you.  
9 DR. LIONBERGER: So your next speaker is  
10 Nikunj Kumar Patel from Simcyp.  
11 Presentation – Nikunj Kumar Patel  
12 DR. PATEL: Thank you, Rob, for introduction  
13 and invitation to present at today's meeting. I  
14 think there was a day-long workshop yesterday on  
15 this topic which I'm going to speak today, so most  
16 of the points I wanted to discuss today were  
17 already discussed and debated. But this is a quite  
18 interesting and evolving area of research which  
19 could help generate product development and  
20 assessment.  
21 So for the people who were not here  
22 yesterday, and who are not from the field, what the

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1 PBPK is, PBPK is physiologically based  
2 pharmacokinetic modeling. And as you can see, when  
3 you talk about pharmacokinetic, there are multiple  
4 types of models which are typically used.  
5 Some of them are empirical, like exponential  
6 models, some compartmental models. Those type of  
7 models are useful when you already have clinical  
8 data and you want to see whether that clinical data  
9 was obtained from one bucket of blood or one bucket  
10 of blood and one bucket of fat, so those kind of  
11 analysis.  
12 But when you look at the PBPK, PBPK is  
13 basically based on the underlying knowledge of  
14 physiology that we have, the current knowledge of  
15 physiology, and you try to port out the system by  
16 giving a drug product. So you are trying to assess  
17 how the drug is going to treat a drug when given in  
18 a particular product or a particular formulation.  
19 So it has quite a good predictive power.  
20 And you can use prior information, so you can start  
21 using it from early development until late stage.  
22 And at each stage, you can try to build more and

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1 more confidence into your model, and finally will  
2 have very good confidence so that you can use it to  
3 make some critical decisions about product and  
4 product changes.  
5 So I think there is a long list of  
6 applications where PBPK has been used, and these  
7 are from the public literature. And this is not an  
8 exhaustive list; there are even more applications.  
9 Some of the critical one are an application in  
10 quality by design or setting of dissolution  
11 specification, establishing IVIVC. This is an  
12 important one.  
13 I think there was a quite good amount of  
14 interest in pediatric and how to assess them.  
15 Maybe PBPK can help to translate adult data to  
16 pediatric, or maybe a disease population. Impact  
17 of food effect as well as impact of proton pump  
18 inhibitor at a gut level drug-drug interaction,  
19 what show bioequivalence.  
20 This is another important point I want to  
21 discuss today, is that assessing the untested  
22 scenarios to fill the gaps in the product

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1 assessment.  
2 Starting with QbD, so I picked up two  
3 examples, but this is not and exhaustive list.  
4 There are multiple examples in the literature. So  
5 the first one is from the FDA group, so I think  
6 this is a nice publication where they put together  
7 a framework in which PBPK modeling can fit into a  
8 quality by design type of assessment.  
9 There is another recent publication from our  
10 group, so I think they set up about, I think, five  
11 or six different examples where modeling and  
12 simulation can be used to answer or address some of  
13 the questions which are typically raised in quality  
14 by design paradigm.  
15 Because of the interest of time, I am not  
16 expected to go in detail. That's why I put the  
17 references. So if you are interested, you can go  
18 and have a look in detail.  
19 But when we look at this and some other  
20 publications, there are many times they fit  
21 parameters because I think the model is not  
22 obviously predictive, so you need to add some of

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1 the known or uncertain parameters.  
2 So the question I have is, basically, when  
3 you do a fitting, because these are the complex  
4 models, and physiology is so variable and  
5 uncertain, maybe you are estimating or fitting a  
6 drug and formulation parameter which might be  
7 accounting for some uncertainty in the physiology.  
8 Maybe your physiology is not right and you are  
9 unknowingly estimating a product parameter to  
10 represent uncertainty in the physiology.  
11 So in those cases, the question is, what is  
12 a qualification criteria? When you fit a  
13 parameter, what should be your endpoint? How do  
14 you decide whether the parameter you fitted is  
15 correct or you are not over-emphasizing on a  
16 particular property?  
17 The second question is that -- I think this  
18 is another ongoing debate and discussion -- what is  
19 a physiology in the PBPK platform? If you look at  
20 different platforms, there are sometimes some  
21 parameters which are arbitrary. Some of them are  
22 assumed.

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1 So the question is, when you use PBPK, do  
2 you need to have reference for physiology which is  
3 being used in a platform -- or by a user, because  
4 they are obviously modifiable -- so do you have to  
5 have a physiology which is scientifically  
6 traceable, which is actually linking to a  
7 physiological measurement based on our current  
8 understanding? Or it can be assumed or arbitrary.  
9 If it is assumed or arbitrary, what is your  
10 acceptance criteria?  
11 Again, it is basically building upon the  
12 previous question. So basically, PBPK is a  
13 probabilistic modeling rather than an accurate, or  
14 basically like compartmental kind. It is where you  
15 have data, you try to explain it. So when it is a  
16 probabilistic science, is it all right to just use  
17 an average human physiology provided in the  
18 platform, or you need to do a population  
19 simulation?  
20 I think there was a quite interest in the  
21 discussion yesterday on global sensitivity  
22 analysis. So that basically says to you that you

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1 need to account for all the uncertainty in the  
2 physiology, as well as variability, to make a  
3 decision. So this is another question. I think we  
4 need to address all these questions before we can  
5 move on to use it as a regulatory submission, too.  
6 Another application is basically translating  
7 adult to pediatric data. So I think this is a very  
8 recent publication from Jennifer Dressman's group.  
9 They developed and validated a formulation, or  
10 basically PBPK model, for fluconazole and  
11 ketoconazole, and then tried to see if they can  
12 translate this information to a children or  
13 basically adolescent patient. So I think there was  
14 some discussion on ontogenies of enzymes.  
15 So basically, these two drugs have been  
16 metabolized by the enzymes, which undergoes  
17 significant modification in early ages. And that's  
18 why the children dose is relatively higher in terms  
19 of milligram per kg as compared to an adult.  
20 Also, the physiology difference is in the  
21 gut. If you use the same formulation in adolescent  
22 or children population, is it going to behave the

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1 same under a given physiological condition,  
2 et cetera? So probably this type of assessment can  
3 be done using PBPK. This was another publication  
4 from Rob's group.  
5 The third publication is from AstraZeneca.  
6 So what they did is they had an immediate-release  
7 formulation and extended-release formulation in  
8 adults.  
9 Also, they had assessed the immediate-  
10 release formulation in pediatric, but they did not  
11 assess, or they did not have clinical data, of XR  
12 in pediatric. So they wanted to see whether they  
13 can make some projections how this is going to  
14 behave in adolescent patients.  
15 So they had an IVIVC established, validated,  
16 and accepted for XR formulation in adults. So they  
17 tried to translate the IVIVC for children, and  
18 tried to make some decision on the dose as well as  
19 the expected population variability.  
20 When we talk about pediatric, I think  
21 pediatric is an interesting area of research as  
22 well as quite challenging, because obviously,

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1 pediatrics are not that much involved in clinical  
2 studies so we do not have sufficient knowledge of  
3 physiology. And there are sometimes scarce and  
4 contradictory data.  
5 So one of them is basically gastric  
6 emptying. So there is some publication which says  
7 that the gastric emptying is related to the age.  
8 Some people say that it is not. So in such case,  
9 what to do? What is the physiology that you should  
10 use?  
11 So probably in such cases there is a  
12 solution that you need to look and understand and  
13 collect all the information available, and then  
14 perform a scientific meta-analysis to see whether  
15 you can find some sort of relationship or not.  
16 We tried to do it, and it is published now,  
17 the paper in DMD, that there is no age relationship  
18 of gastric emptying. However, there is a strong  
19 relationship with the food, and the food taken by  
20 pediatric at various ages is different. So  
21 basically the food, because of the type of food  
22 they eat at different ages, probably that is why

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1 they are seeing different gastric emptying time,  
2 not necessarily because of the age.  
3       Again, when you have unknown or uncertain  
4 parameter, what should be the qualification  
5 criteria? When can you accept the model?  
6       This is a third application predicting the  
7 food effect. So I think there are a number of  
8 examples here, but the main question is, sometimes  
9 you have some parameters which are not  
10 experimentally measured, and people tend to use  
11 QSAR model to estimate those parameter. Or  
12 basically you can estimate something from chemical  
13 structure -- for example, permeability or PK -- and  
14 use it to make a prediction.  
15       I came across quite interesting example  
16 recently, and they used QSAR. But when used  
17 experimental data, their conclusion was totally  
18 different. So you need to make sure, when you have  
19 some parameters, whether they are acceptable. If  
20 not, then are you going to recommend them to go and  
21 measure experimentally? Or what is the minimum  
22 number of parameters that can be estimated?

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1       Another application is IVIVC. So I think  
2 with PBPK there was a lot of discussion, and this  
3 is one of the potential area that can have more  
4 confidence. So we tried to compare PBPK with  
5 conventional approach and I think I don't have lot  
6 of time to go in detail. But the same approach was  
7 taken up by a colleague in FDA, Bipin and Marilyn.  
8 So they basically tried to assess the application  
9 of mechanistic IVIVC at population level. They had  
10 access to individual data.  
11       They perform two type of validation. Leave  
12 one formulation out, which is typical. So every  
13 time, they left one formulation out and tried to  
14 see how well the IVIVC predict for an unknown  
15 formulation. And they also performed a bootstrap.  
16       But I think, on top of that, they performed  
17 an interesting analysis because the purpose of  
18 IVIVC is to predict for an unknown person or  
19 unknown population. So they left one individual  
20 out to see whether the IVIVC can predict all three  
21 formulations for a missed-out subject.  
22       This is another application where they tried

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1 to assess the equivalence at PD level rather than  
2 PK. So you can see that for ibuprofen, the PK  
3 level, there is a strong discrimination. But  
4 because of the flat response profile, there is not  
5 much discrimination.  
6       This is a final and very important example I  
7 wanted to discuss. So again, we generally assume  
8 that the bioequivalence at healthy subjects is  
9 valid for a patient population. But when you look  
10 at it for ketoconazole and posaconazole, because of  
11 the behavior of the drug and formulation, if the  
12 drug was bioequivalent in fasted condition, does  
13 not necessarily mean that they are equivalent in  
14 fed condition.  
15       There are certain conditions which are more  
16 discriminatory than another condition. So probably  
17 this type of simulation can also help what should  
18 be the bioequivalent study design which can allow  
19 you to discriminate to the best possible way for  
20 different formulation.  
21       So to summarize, we need to have more case  
22 examples to improve the confidence in PBPK. The

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1 second and most important is that we need to have  
2 more than qualification criteria. What is  
3 acceptable model. Then we need to establish good  
4 practices to improve the application of PBPK in  
5 regulating modeling because at the moment, if you  
6 look, there are multiple types of models available  
7 and people use PBPK with a lot of different things.  
8 So you need to have some sort of an idea of what is  
9 good practice.  
10       We need to understand more about  
11 interoccasion variability. I think there was a  
12 discussion, and FDA is already funding some grants  
13 to do and understand more about how the human  
14 physiology changes on different occasion, and how  
15 the formulation will behave.  
16       I think we need to also have some more  
17 research on modified and enabling formulation, as  
18 well as assessing the mechanistic assessment of  
19 excipient impact; for example, cyclodextrin  
20 exchange as well as some of the enabling  
21 formulation where polymer is used to inhibit  
22 precipitation, et cetera. And thank you.

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1 DR. LIONBERGER: Thank you.  
2 DR. UHL: So I'll ask my same question I've  
3 asked many times. Your previous slide had at least  
4 half a dozen or more suggestions. If you can  
5 answer this now, what would be your number one  
6 priority, or how would you recommend prioritizing  
7 that and submit it to the docket?  
8 DR. PATEL: Well, if given a choice, I would  
9 invest all \$20 million in this so we sort it out.  
10 (Laughter.)  
11 DR. UHL: Well, that's true. But you have a  
12 lot of suggestions related to PBPK.  
13 DR. PATEL: Yes.  
14 DR. UHL: So that, in the context of generic  
15 drug development, which do you think would be most  
16 impactful?  
17 DR. PATEL: I think, with the current status  
18 and based on some discussions yesterday, I would  
19 say we need to first arrive at what is a qualified  
20 model and what are the good practices. So once we  
21 set up our baseline where the model works and where  
22 it doesn't, with current knowledge, then we can

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1 move further.  
2 So I think for a first priority, I think we  
3 need to set up some sort of a model qualification  
4 criteria and what is acceptable model, what are the  
5 good practices, and then see how well the  
6 prediction performs.  
7 So basically, there needs to be some  
8 assessment of case examples where you can assess in  
9 what cases you have good confidence or less. So  
10 there needs to be more research on generating case  
11 examples and generating some good practice  
12 guidelines, and then the rest of them can be  
13 followed up.  
14 DR. LIONBERGER: Thank you very much. Oh,  
15 I'm sorry.  
16 MS. PEREZ: You mentioned that we need more  
17 research and then sort it that way. But when you  
18 say we need more research, are you suggesting the  
19 FDA does more research on this, or the industry, or  
20 yourself? Who is going to conduct this research  
21 and come up with these parameters for the industry?  
22 DR. PATEL: Yes. I think, yes, that's a

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1 very good question. So I think if you look at the  
2 points, there are certain points where I think we  
3 need more regulatory input. For example, what is  
4 good practice? What is good model qualification  
5 criteria? Where we need more input from regulators  
6 and based on your own understanding or assessment?  
7 Certain of research items, like interoccasion, it  
8 can be funded by government or it can be funded by  
9 academia or industry, et cetera.  
10 So there are certain aspects which can be  
11 done independent of regulatory funding, but there  
12 are certain aspects where we need at least some  
13 sort of cooperation between industry, academia, and  
14 regulators to come up to a conclusion that -- and  
15 this is not an easy question to answer. What is  
16 qualified model is ongoing debate and discussion.  
17 So it requires, really, a strong effort.  
18 I think I forgot to mention about the OrBiTo  
19 project, which is an interdisciplinary project  
20 where a lot of effort has gone in to see where the  
21 models can predict and where it cannot, what should  
22 be the qualification criteria, and what should be

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1 the good practices, et cetera. So I think there is  
2 a need to have an interdisciplinary research  
3 approach to arrive at some conclusion on what is  
4 the good practice.  
5 MS. PEREZ: Thank you.  
6 DR. PATEL: Okay. Thank you.  
7 DR. LIONBERGER: Thank you very much.  
8 So our next speaker is Russ Rackley from  
9 Mylan.  
10 Presentation – Russ Rackley  
11 MR. RACKLEY: Okay. Thank you. I'm Russ  
12 Rackley. I'm head of global PKDM at Mylan  
13 Incorporated. And I want to thank you all for  
14 letting me make a brief presentation today. These  
15 are my views and not necessarily those of the  
16 official opinions or policy of Mylan.  
17 But I will speak to the challenges with the  
18 demonstration of statistical noninferiority of  
19 adhesion and irritation for transdermal drug  
20 delivery systems using the OGD bioguidance method.  
21 So I'll get right to the issue here. The  
22 problem with the current adhesion or irritation

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1 noninferiority testing is based on using OGD's  
2 recommended scoring scale. When a product scores  
3 very well or performs well, the adhesion or  
4 irritation scores are zero or approach zero.  
5       So for the current guidance, the  
6 noninferiority margin is proportional to the mean  
7 score of the RLD. And the consequence of that is  
8 its noninferiority margin also then approaches  
9 zero.  
10       So one thing, one comment: In my experience  
11 of 15 years at Mylan, and seeing a lot of evolution  
12 over time, I think this may not initially have been  
13 as much of a problem. But we're seeing more RLDs  
14 that are performing very well, and this is where  
15 the challenge comes in.  
16       So the requirement is forcing generics  
17 practically to perform as a superior product  
18 relative to the RLD and/or could potentially  
19 require extraordinary powering considerations. And  
20 that's in a space, as I'll illustrate, where  
21 there's little room to improve already on what we  
22 consider good product. So Mylan believes the

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1 current guidance, although again not intended to do  
2 so, effectively serves as an inappropriate block to  
3 generic approvals.  
4       So I'll briefly touch on the criteria here,  
5 the statistical test, as outlined in the current  
6 guidances. And this is for adhesion and/or  
7 irritation. Basically, we're looking at a one-  
8 sided test for the 95 percent upper confidence  
9 interval based on the mean test score minus  
10 1.25 times the mean reference score. And this  
11 should be less than or equal to zero.  
12       The point I just want to make on this  
13 equation is it could be rearranged so that you  
14 could show the mean reference score in the  
15 denominator. So as you have a mean reference score  
16 that approaches zero, as we're starting to see more  
17 and more of, this greatly inflates the metric such  
18 that it becomes very stringent to meet the criteria  
19 against any kind of constant or criteria for  
20 noninferiority.  
21       I'll try to illustrate that a little bit  
22 with this graph. I've illustrated here a graph of

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1 test mean irritation on the Y-axis and reference  
2 irritation on the X-axis. And there's a line of  
3 identity there you'll see that goes where the test  
4 and reference would be equal. The dashed red line  
5 shows where the criteria for noninferiority would  
6 be, and it's proportional based on the ratio of  
7 1.25.  
8       So as you approach to zero, this margin  
9 effectively diminishes. So test products are  
10 forced into a performance at very low levels, so  
11 around a mean score reference of 1. There's a  
12 little space there to operate or perform relative  
13 to the same level as the reference product.  
14       But as the reference scores become lower and  
15 lower, this forces the performance of the test  
16 product -- the generic, that is -- to be lower and  
17 lower again and squeezed into an area where there's  
18 little room for improvement. And the performance  
19 is superior in that there has to have almost a  
20 lower score, or does have to have a lower score.  
21       I'm going to illustrate this with two  
22 examples based on some actual data. This is

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1 example one, illustrating good adhesion  
2 performance. On the left panel is data for the  
3 generic, and on the right is the reference listed  
4 drug. And this is based on 36 subjects that wore a  
5 high-strength patch for one 24-hour interval.  
6       Adhesion was checked at 4-hour intervals per  
7 the OGD adhesion scale. And the scale score is  
8 again zero -- it was the best performance -- 1, 2  
9 and 3. One is 90, or zero is greater than  
10 90 percent, greater than or equal to 90 percent.  
11 One is 90 to 75. Two is 75 to 50. Three is less  
12 than 50 percent adhesion.  
13       Over at the first check, at 4 hours, there's  
14 very good performance. Nearly all subjects have a  
15 score of zero. There's good adhesion. As time  
16 goes on, there's a little bit of disadhesion over  
17 time, and you'll see some distributions go out to  
18 scores of 1, 2, and 3, and so forth.  
19       If you sum these scores over time, you'll  
20 get the cumulative adhesion scores for each  
21 product. And that's illustrated here graphically  
22 in this bar chart, with the blue bars representing



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1 the test product, the generic. And it looks like  
2 the lighter bars up there -- maybe I'm colorblind.  
3 On here it's blue, but up there it's grey. It's  
4 switched. But anyway, the left side is the test.  
5 The right side for each pair is the reference.  
6 The point here is that there's a very  
7 good -- there's a high proportion of zero scores in  
8 this dataset. Distributions are fairly comparable  
9 as you go out and tail out. So overall, this  
10 represents very good-performing products.  
11 So in fact, the total observations for the  
12 test product was such that 86 percent of  
13 observations had a score of zero, again accounting  
14 for all observations. The reference had 85 percent  
15 of all scores equal to zero.  
16 We look at the mean adhesions on these, and  
17 they're identical at 0.181. And we look at the  
18 metric here, and the upper confidence interval is  
19 0.0225, which is greater than zero, so it fails the  
20 metric in this case.  
21 If you consider this amount, this interval  
22 above zero, it effectively relates to -- the test

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1 would have had to perform about 12 percent or more  
2 better to shift everything down and meet the  
3 criteria. So that's what I'm getting to, is in  
4 terms of -- there seems to be push to a superior  
5 performance aspect.  
6 Moving on, and these are busy slides, but  
7 this is a similar kind of situation where we're  
8 getting moderate scores, in this case irritation.  
9 It could apply to adhesion as well. This was a  
10 study in which 36 subjects wore a patch daily over  
11 21 days with same site application. Again, the  
12 left side is the generic. The right side is a  
13 reference.  
14 Starting out, both products have  
15 roughly -- about a third of the subjects had scores  
16 of zero. So even after one application, there's  
17 very few subjects that --there's a minority of  
18 subjects that had no irritation, and more that had  
19 barely observable irritation. And that  
20 distribution shifts over time as the study's  
21 conducted to 21 days.  
22 Again, if we sum the scores over 21 days per

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1 each of the observed irritation scales, scores in  
2 this case, you get the bottom score, which is a  
3 cumulative irritation value. And that's  
4 illustrated again the distribution in this chart.  
5 So you'll see the preponderance of scores.  
6 Again, on the left is the generic. The right is  
7 the reference. Predominately scores of 1, which  
8 again is barely perceptible erythema on the dermal  
9 scale; or a 2, which is definite erythema, or could  
10 be a combination of scores of dermal and other  
11 scores. But the point is, there is a very similar  
12 pattern and distribution, again predominant around  
13 1 and 2 for most subjects across the study.  
14 If we look at the summary on this, you'll  
15 see similar mean scores of about 2. The upper  
16 confidence interval is minus .41, which is well  
17 below the criteria, so it would pass. There's  
18 enough space there in that interval such that you  
19 could almost be 15 to 20 percent higher relative to  
20 the reference and it would probably pass. And  
21 that's normal for a bioequivalence type of  
22 consideration, but this is one-sided with respect

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1 to noninferiority.  
2 The current OGD guidance method suffers from  
3 the use of nonlinear discrete scale, good adhesion  
4 or irritation results, and datasets consisting  
5 largely of zeros. And as a result, as the  
6 reference approaches zero, the margin essentially  
7 disappears, which again forces the generic to  
8 essentially perform in a superior manner and/or  
9 could require extraordinarily high numbers of  
10 subjects from a powering point of view.  
11 Thus, there's a need for an updated  
12 noninferiority testing method for both adhesion and  
13 irritation that will span the spectrum of RLD  
14 performance, particularly for well-performing RLDs,  
15 which predominately score out at zero, according to  
16 the scales.  
17 We've contemplated some alternatives. One  
18 would be just change the scale for adhesion so it  
19 directly relates to performance of the product. So  
20 you could use any kind of score, but as long as it  
21 relates to in this case it could be a 9 or 95 down  
22 to a lower score, but relates proportionately to

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1 the degree of adhesion observed in the clinic  
2 during the study. And I just note this because the  
3 EMEA has endorsed this approach, and we feel this  
4 method should be considered in reevaluation.  
5 A more simplistic approach might be simply  
6 to adjust the scale. Rather than start it at zero,  
7 start it at 1. This is effectively adding 1 to  
8 your overall scoring. So this would compensate for  
9 the problems that we have with the metric, and it  
10 would be a very simple solution to implement, and  
11 would accommodate the issue for both irritation and  
12 adhesion.  
13 So questions? Does OGD agree with the  
14 current metrics for noninferiority testing for  
15 adhesion and irritation that need to be modified to  
16 accommodate all types of product responses? And  
17 can OGD promptly provide an alternative method for  
18 generic companies to fairly compare their products  
19 to the RLDs across the full range or spectrum of  
20 RLD responses anticipated for both adhesion and  
21 irritation?  
22 Again, acknowledge this has been an ongoing

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1 consideration, but we are seeking some  
2 consideration. And I have already pre-prioritized  
3 this as an issue for recommendation. So I'll take  
4 some questions.  
5 DR. UHL: Yes. So can you tell me what your  
6 priorities are, then? Because you actually asked  
7 us questions, which is not the forum in a Part 15  
8 hearing. The agency gets to ask the questions. So  
9 if you want to prioritize, that would be great.  
10 And I have a follow-up question for you as well.  
11 MR. RACKLEY: Okay. Really, it's coming  
12 back to I prioritized these questions for the  
13 panel to consider. So really, the issue is  
14 fundamental. It's around the scales that the OGD,  
15 I think, use. It relates to use of zero for  
16 identifying with good performance, which is  
17 somewhat counterintuitive, I think. But it depends  
18 on which way you look at the scales.  
19 So it's almost as though any other score  
20 other than zero might work in this situation.  
21 There are other ways to go about it using different  
22 perhaps statistical approaches or other

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1 considerations. But I see the root of the issue as  
2 being how to address the scale itself.  
3 DR. UHL: Okay. So I appreciate that. I  
4 just want some clarity on your concern here because  
5 on your second slide, you say that this is for  
6 good-performing products. So I just want to  
7 understand what good-performing products means. Is  
8 that products that have good adhesion?  
9 MR. RACKLEY: Yes.  
10 DR. UHL: Okay. So for --  
11 MR. RACKLEY: And/or low irritation.  
12 DR. UHL: Okay, so for product --  
13 MR. RACKLEY: So clinically speaking, you  
14 want a patch that has great adhesion, performs  
15 well, and it consequently will score as a zero. It  
16 should have low irritation as well, ideally, and  
17 will consequently also score as a zero.  
18 So the problem exists the way the guidances  
19 are written for both adhesion and irritation in  
20 that scores of zero reflect good performance of the  
21 product, of the RLD, is what drives the criteria  
22 here.

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1 DR. UHL: I appreciate that. So what you're  
2 saying is that this aspect of the noninferiority  
3 testing problems that you're pointing out are  
4 relevant for patches that are highly adherent?  
5 MR. RACKLEY: Yes, highly adhering, low  
6 irritating.  
7 DR. UHL: Right.  
8 MR. RACKLEY: This occurs, as I  
9 mentioned -- we see this more and more, I think,  
10 for some RLDs. They may have one or both of these  
11 parameters that perform that way. So it presents a  
12 problem, that the probability of encountering this  
13 is fairly high.  
14 That's where we see the issue, how to  
15 address this when RLDs -- when you have to go up  
16 against an RLD that forces you to want to perform  
17 better, but there's little room to improve on a  
18 product that's already getting the best possible  
19 score sometimes.  
20 DR. CONNER: Yes. Since this a regulatory  
21 research meeting, in this particular topic, what  
22 are your research ideas? Where would you like us

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1 to focus research dollars on addressing this, or  
2 related issues to this? Do you have any kind of  
3 projects or things that need -- questions that you  
4 feel need to be answered through research?  
5 MR. RACKLEY: There's a wealth of data out  
6 there already that have been, I'm sure, submitted.  
7 And I believe this is a problem that is throughout  
8 the industry. So datasets are there that could be  
9 taken and potentially used in evaluations via  
10 simulations, bootstrapping considerations, that  
11 sort of thing, to really explore how best to -- if  
12 one were to modify either the scale or the metric,  
13 how to modify that sort of data.  
14 So the question would be, then, how would  
15 you disseminate or make that data available? It  
16 needs to be relevant data relative to actual kinds  
17 of observations that are seen in these kinds of  
18 studies.  
19 DR. CONNER: Also, I think, one of your  
20 first slides you specified the current  
21 noninferiority method that we're using. But I  
22 think that we've gone beyond this. This is not

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1 entirely 100 percent accurate since we've added a  
2 90 percent role on top of that, which I think we  
3 have actually discussed with some of your -- some  
4 of the GPhA member companies who had issue with  
5 this.  
6 So this isn't the complete story on how we  
7 handle these, although, granted it is still an  
8 issue, and it's still worthy of pursuing. But it's  
9 not entirely 100 percent accurate, as far as that  
10 goes.  
11 MR. RACKLEY: Well, I don't know that  
12 it -- yes, I didn't know if that was necessarily  
13 public knowledge, so I did not really comment on  
14 that. But I don't know that it necessarily, as I'm  
15 referring to this, really deals with the full  
16 spectrum of RLD responses, so from 100 percent  
17 down -- or from scores of zero to whatever the  
18 maximum score is.  
19 So you can think of this as percentage of  
20 adhesion if you want to, so from 100 percent  
21 adhesion down to zero percent adhesion. So I don't  
22 know that it fully covers. I mean it covers one

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1 end. It's not a problem on the other end. There's  
2 still a potential problem in the middle.  
3 DR. LIONBERGER: Thank you.  
4 So our next speaker is David Schoneker,  
5 representing IPEC Americas.  
6 Presentation -- David Schoneker  
7 MR. SCHONEKER: I'd like to thank the FDA  
8 for giving me the opportunity to speak on a topic  
9 near and dear to us at IPEC Americas today. We've  
10 heard a lot throughout the day, almost from every  
11 speaker, about the importance of excipients in a  
12 lot of different ways -- the importance to  
13 formulation science, manufacturing science,  
14 pediatrics. Ajaz brought up the need for simple  
15 versus complex formulations.  
16 I'd like to put that into perspective with  
17 what's really happening out there that I'd like to  
18 talk about. And that is, we talk about the need  
19 for more focus and more science in the area of the  
20 impact of excipients on formulation quality and  
21 performance, which is what's really key.  
22 But before formulators start picking

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1 excipients for formulations based on that kind of  
2 data, the first thing they have to address is the  
3 safety of the excipient. So that's actually the  
4 first and the biggest driver that's actually going  
5 into drug development today.  
6 Unfortunately, due to the inappropriate use  
7 of some of the existing tools, and the lack of some  
8 new tools that are needed, we're finding that this  
9 is driving generic drug development, in some cases,  
10 in the wrong direction.  
11 Now, I'd like to coin a new term today.  
12 We've heard a lot about QbD, QbR. I'd like to talk  
13 about QbI. And QbI is quality by IID. Okay?  
14 Because that, as I go around the country and around  
15 the world talking to generic companies, is what's  
16 driving how many generic drug formulations are in  
17 fact developed. And I'll talk more about that as I  
18 go through the slides.  
19 So IPEC Americas, as with GPhA, we have a  
20 lot of members. We have over 80 member companies  
21 here in the US, over 350 member companies around  
22 the world, and we represent many of the biggest

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1 generic OTC innovator drug companies, most of the  
2 major excipient companies all over the world.  
3 So some of our key concerns, getting at my  
4 points earlier, is that we believe that some of the  
5 current OGD policies and guidance for generic drugs  
6 related to excipient safety review are really not  
7 science- and risk-based.  
8 We like to talk a lot about science- and  
9 risk-based, but what we see actually happening is  
10 not necessarily so, based on good toxicology and  
11 good safety reviews used throughout the world.  
12 It's not really aligned sometimes even with the way  
13 these materials get looked at by other areas, even  
14 within the FDA, from the new drug side, to CFSAN,  
15 to the cosmetic folks.  
16 The current policies and guidances, such as  
17 the RTR guidance and the controlled correspondence  
18 guidance, related to where it talks about the use  
19 of the IID are actually creating barriers to  
20 innovation and significant confusion throughout the  
21 industry.  
22 For example, in the RTR guidance, it says

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1 specifically that any use of novel excipients means  
2 that it shouldn't be a generic drug, it should be a  
3 505(b)(2). Okay? Now, I'm going to come back to  
4 the fact that novel excipients can be defined a lot  
5 of different ways, not just new chemical entity  
6 type of excipients. But I'll come back to that.  
7 Now, IPEC Americas and GPhA has had a  
8 working group, and we've been working very closely  
9 with folks at FDA, a combination of people from  
10 many different departments in OGD and many other  
11 groups. And we've been working since 2011 to not  
12 only make improvements in the IID, but also to try  
13 to address some of the policies around how this  
14 gets used in the area of drug development.  
15 Unfortunately, we've submitted a lot of  
16 information, had a lot of discussions, but some of  
17 the most key decisions I'll touch on today have  
18 really still not been made that are needed to be  
19 implemented by FDA, even here in 2016. So we feel  
20 that there is a need on the one hand for better  
21 coordination of some of these concepts between OPS  
22 and OGD and the industry.

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1 Now, putting it in context of the questions  
2 that were asked for this particular session, I'm  
3 going to focus on number 1, 5 and 6. So in the  
4 area of technical advancements that are needed to  
5 overcome specific barriers, again we believe that  
6 the current excipient safety review and the  
7 IID-related policies are stifling innovation.  
8 It's wasting FDA resources, and resulting in  
9 the development of non-optimized generic drug  
10 product formulations. Now, I'll come back to that  
11 in a minute because that's a very interesting  
12 point.  
13 But on number 5, what I'll be talking about  
14 is the need for a read-across approach to excipient  
15 toxicology review that is needed for the evaluation  
16 of excipient families. We tend to call that the  
17 family approach within IPEC. And that's needed in  
18 order to facilitate streamlined assessments based  
19 on good science.  
20 This practice is the most common practice  
21 used by regulators around the world, and it's  
22 already used, as I mentioned earlier, in many other

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1 parts of the FDA to essentially bracket families of  
2 things like polymers where all the toxicology is  
3 the same. That's not necessarily how it gets  
4 applied in generic drug development.  
5 The last one related to strategies for  
6 enhancing equivalent risk management. We believe  
7 that the acceptance of this family approach, and  
8 the need for an independent novel excipient  
9 qualification process, could speed up generic drug  
10 development, improve drug quality and performance,  
11 and enhance the use of advanced manufacturing  
12 techniques, such as continuous manufacturing.  
13 Now, the ANDA process, the impact that the  
14 IID has on this -- we believe, again, some changes  
15 are needed to improve the efficiency of the ANDA  
16 process for excipient safety review. This would  
17 help the agency and industry meet GDUFA goals,  
18 apply science-based risk assessment principles,  
19 minimize reviews of redundant excipient toxicology  
20 information, and reduce confusion regarding the  
21 IID.  
22 Now, the current IID and the associated

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1 policies, as it's being applied today, we believe  
2 is insufficient to support efficient drug  
3 development and approval, and we must streamline  
4 this process and use good science to assess what is  
5 the real risk.  
6 The real risk, in most cases, many commonly  
7 used excipients are extremely safe. There's really  
8 not much of a safety issue when you're using  
9 existing materials, even at higher levels,  
10 et cetera, as I'll talk about.  
11 So some of the new uses of existing  
12 excipients that come up in drug development, and  
13 novel excipients -- and I'll say that are not new  
14 chemical entities because FDA's own definition of a  
15 novel excipient includes new chemical entities,  
16 coprocessed excipients, higher levels of existing  
17 excipients, new routes of administration,  
18 coprocessed excipients, et cetera.  
19 If we can use these materials more  
20 effectively, and again, recognizing that new  
21 chemical entity type of excipients might be more  
22 appropriate for innovator drugs, but a lot of these

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1 other types of novel excipients are being avoided  
2 in many different ways.  
3 If we can use these, it would enhance high  
4 quality generic drug development at equivalent  
5 performance to innovator drugs in many cases. It  
6 would also allow us to improve manufacturing  
7 productivity and help control the cost of the  
8 generic drugs.  
9 Now, this next point I want to elaborate on  
10 just a bit. I said many generics are being  
11 designed with less than optimum formulations due to  
12 barriers in the excipient safety review process for  
13 ANDAs.  
14 I get out to many, many generic companies  
15 all around the world. I just came back from a week  
16 in India. I talked to hundreds and hundreds of  
17 formulators, and I've talked to many here in the  
18 US.  
19 The thing I hear consistently from the  
20 majority of these people is that their companies  
21 have a policy in place that says under no  
22 circumstances should a formulator use any excipient

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1 at a level higher than what's in the IID, and since  
2 they don't know what the MDI is, that their MDI  
3 shouldn't exceed what's in the IID, which doesn't  
4 make a lot of sense.  
5 But that's what's actually happening, and  
6 people have told me they have formulated  
7 non-optimized products just because they want to  
8 stay under the IID, even though they know they  
9 could use more of a particular excipient and get  
10 much better performance. Instead, they use, many  
11 times, multiple grades of the same excipient so  
12 they can stay under the grade level that's listed,  
13 which adds complexity and unknowns to the  
14 situation.  
15 So the process should be consistent, we  
16 believe, with risk management concepts, good  
17 science and global toxicology practices, and  
18 quality by design principles. Some of the key  
19 things that we're looking for is, we'd like to have  
20 a standardized approach for supplying inactive  
21 ingredient information to streamline the submission  
22 and review process. We've already worked on some

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1 of this. We'd like to see it implemented.  
2 We'd like to use this -- again, the excipient  
3 family approach -- to facilitate common pharm/tox  
4 evaluations for related excipients; prioritize a  
5 one-time review of excipient families where in fact  
6 the same exact toxicology will always apply to  
7 everything in that family, regardless of the  
8 context of use; and revise FDA guidance documents  
9 by correcting contradictory and inconsistent  
10 information.  
11 So what's an excipient family? Well, again,  
12 I alluded to this before. It's many times many of  
13 the families that are the most common excipients  
14 out there, such as polymers like hypromellose,  
15 et cetera, are chemically similar but may have  
16 various grades in the family that are all covered  
17 by the same toxicological standpoint.  
18 Hypromellose is a great example. JECFA, and  
19 in fact CFSAN, has already agreed that there is no  
20 safety difference between any grade of  
21 hypromellose. In the food arena, you can eat up to  
22 20 grams. FDA's approved 20 grams. JECFA of WHO,

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1 the Joint Expert Committee on Food Additives, said  
2 there's no reason to even put a limit on  
3 hypromellose, so their ADI is not specified.  
4        Yet in the IID, we have many grades of  
5 hypromellose, with levels as low as 40 milligrams,  
6 and people being asked for full toxicology studies  
7 on that particular grade of hypromellose to justify  
8 100 grams, or 100 milligrams. It doesn't make any  
9 sense.  
10        So I'll try to finish up because I know I'm  
11 about out of time here. Benefits of the family  
12 approach. Transparency to drug formulators on  
13 maximum excipient use levels by route, as supported  
14 by tox data.  
15        This would minimize need for multiple FDA  
16 reviews of the same toxicology data once a maximum  
17 use level has been accepted. It could expedite FDA  
18 review of ANDAs, minimize errors and resources to  
19 maintain the IID, and reduce the complexity of the  
20 IID.  
21        So our ask, if you will -- and I only have a  
22 couple, so it should be easy to see the priority

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1 here -- we really believe that there needs to be a  
2 formalized acceptance of a lot of the things we've  
3 already presented to the FDA related to this family  
4 approach. We pretty much presented all the science  
5 that exists to justify this.  
6        If needed, we feel that through the  
7 regulatory sciences initiative, if there's some  
8 science that people feel is needed to be able to  
9 make this decision, we would like to see whatever  
10 studies it is that are needed to make this decision  
11 done under this initiative so that we could move  
12 this forward.  
13        We'd also like to see revision of the RTR  
14 and controlled correspondence guidance to  
15 facilitate innovation related to the use of novel  
16 excipients that are not based on a new chemical  
17 entity, and work with industry to investigate the  
18 development of an independent novel excipient  
19 qualification process outside of the drug approval  
20 process. This could save everybody a lot of time.  
21        Finally, I'd agree with GPhA, there's a need  
22 to set up industry working groups to look at the

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1 priorities and investigate specific projects beyond  
2 what we've done in the past. So with that, I'd  
3 like to stop and ask for any questions.  
4        DR. LIONBERGER: Thank you.  
5        MR. SCHONEKER: Thank you.  
6        DR. UHL: So based on your comments specific  
7 to the RTR and the controlled correspondence  
8 guidance, did IPEC send comments to the docket when  
9 those were published?  
10        MR. SCHONEKER: Multiple times. We brought  
11 it up in every one of our meetings. We've sent  
12 comments in. We've been talking about it since  
13 2011 in every venue we can. But we haven't been  
14 able to get a decision on some of these things, and  
15 that's what we're not understanding.  
16        If there is some science that's needed to be  
17 able to get the decisions made internally that are  
18 necessary, let us know what it is, and maybe we can  
19 work through this venue or through any other venue  
20 to get that science there that's needed, if there's  
21 anything.  
22        We're not sure what is needed because this

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1 approach we talk about here is what's used by every  
2 regulatory agency in the world, and we've brought  
3 in world-class experts to testify to that already.  
4        DR. UHL: Thank you. I have a follow-on  
5 question unrelated to that. Your third bullet is  
6 an independent novel excipient qualification  
7 process. So could you elaborate a bit on what that  
8 would look like?  
9        MR. SCHONEKER: I could. And in fact, we've  
10 already started some initial discussions on that.  
11 We did meet with Susan Zuk. We've put a meeting  
12 together with some of the FDA toxicologists, both  
13 from OGD and the new drug side, back last year to  
14 initiate a discussion on how could we set something  
15 like this up.  
16        What came out of that discussion was, this  
17 is something that -- it's different, but it could  
18 look something like what goes on with the biomarker  
19 qualification process, where you could have  
20 something where there's an intended use  
21 established, an intended exposure level  
22 established, and then the safety data could be

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1 presented to an appropriate group that could then  
2 make a recommendation not to approve the material  
3 but to qualify the material for those applications  
4 up to a specific use level, whatever, based on the  
5 actual safety data that exists for the excipient.  
6 It is a situation that could be funded  
7 through user fees or through other mechanisms. We  
8 proposed a lot of those things. And what came back  
9 was there was an interest. I know I've talked to  
10 Lawrence Yu about this as well, and what we're  
11 doing in industry is both IPEC and the IQ  
12 Consortium is having some discussion. And we've  
13 been having discussions with GPhA as well, about  
14 how we could actually now take that concept that we  
15 talked about and make a proposal to FDA for you to  
16 review about how we could set something like that  
17 up that would be an independent review process.  
18 Because part of the problem we have here is  
19 until we can have the excipient safety not become  
20 an issue, that ends up dominating the formulation  
21 discussions way beyond what the actual technical  
22 issues are, where we should be spending the

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1 resources about how to make better formulations,  
2 how to improve quality by design, prepare things,  
3 or even develop excipients that would enhance  
4 things like continuous manufacturing.  
5 But without addressing some mechanism to get  
6 beyond this sort of safety concern that the generic  
7 industry has, then nobody touches that. I guess  
8 you could say it's QbF, quality by fear in that  
9 situation. So somehow we've got to resolve that  
10 because otherwise we're just going to keep fighting  
11 that all the time.  
12 DR. UHL: Good.  
13 MR. SCHONEKER: Thank you.  
14 DR. BOAM: Hi, David. Thanks for the  
15 presentation. With respect to the family approach,  
16 I was going to ask whether you or your organization  
17 had a chance to follow up on thoughts about using  
18 the critical path innovation meeting approach to  
19 try to have discussions about that? And if you've  
20 gotten some feedback on that, what feedback you  
21 might have gotten.  
22 MR. SCHONEKER: Well, and I know -- yes.

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1 Well, Susan had told us that that might be an  
2 avenue to pursue, and we're actually having  
3 internal discussions now, both within IPEC, the IQ,  
4 and GPhA as well, is how can we come into that  
5 process. Again, it's not a process we're that  
6 familiar with yet, but we want to get familiar and  
7 then try to utilize that process in the near future  
8 to make these proposals I was talking about.  
9 Because we think that's a great idea. And  
10 again, we think that could tie into some of the  
11 science objectives too, because if there's some  
12 studies needed, some science that's needed, some  
13 need to address guidelines, all of this could be  
14 focused in there. Thank you.  
15 DR. LIONBERGER: All right. Thank you very  
16 much.  
17 MR. SCHONEKER: Okay, thanks.  
18 DR. LIONBERGER: We will now take a  
19 15-minute break, and we'll reconvene at 3:20.  
20 (Whereupon, at 3:05 p.m., a recess was  
21 taken.)  
22 DR. LIONBERGER: Welcome back, everyone.

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1 Please take your seats so we can begin the final  
2 session of this meeting.  
3 Our next speaker is Bahman Asgharian from  
4 Applied Research Associates. Welcome.  
5 Presentation – Bahman Asgharian  
6 DR. ASGHARIAN: Thank you for the  
7 opportunity to be here. I would like to present a  
8 research idea that has been made possible by recent  
9 advances in our computing resources and image  
10 technologies.  
11 I will be talking about the reconstruction  
12 of lung airway trees to detect earliest stages of  
13 disease in the children with lung disease, and  
14 following it up by computation of three dynamic  
15 calculations to study lung ventilation and drug  
16 delivery. This type of work actually complements  
17 PD/PK modeling in the sense of reducing uncertainty  
18 for the dose that goes as input to the PK or PDPK  
19 models.  
20 So the motivation for the proposed idea is  
21 to explore novel airway modeling techniques to  
22 detect lung disease at earliest stages before the

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1 disease has a chance to damage or destroy lung  
2 airways, and look for that, the window of  
3 opportunity for drug intervention and treatment.  
4 Also, use the modeling technique to explore  
5 new ways to target drug to the affected sites where  
6 we know, because of the damage, the lung is  
7 resistant to airflow and drug getting there. And  
8 at the same time, reduce the drug delivery to the  
9 sites that it typically goes to, undesired sites,  
10 and as a result, minimize the side effects.  
11 3D modeling of the lung children, it cause  
12 high-resolution imaging. And this imaging actually  
13 is available already from other studies for both  
14 the diseased lungs and for healthy lungs of  
15 children.  
16 The idea I am proposing would add these  
17 knowledge gaps that have been identified by the FDA  
18 in terms of physiological variability within a  
19 subject, leveraging complex models and computing,  
20 model validation when we don't have data, and  
21 understanding the physiology in subpopulation -- in  
22 this particular case would be children with lung

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1 disease.  
2 The example I will be presenting is cystic  
3 fibrosis. Cystic fibrosis is a chronic disease  
4 which targets the lungs mainly and start with the  
5 upper lobes of the lung. So the disease  
6 actually -- the changes to the lung due to the  
7 disease starts early in life.  
8 The way it's being diagnosed is they take  
9 CTs of the lungs, and those CT images we can use  
10 for the ideas I am proposing. So the treatment for  
11 this disease is to try to reduce the severity of  
12 the symptoms and slow the progression. However,  
13 intervention is the key. You have to intervene  
14 early, before the lung airways are damaged.  
15 So the problem is that detecting this  
16 disease at the earliest is a challenge. We have to  
17 look for biomarkers, variables, that can allow us  
18 to do that. The objective would be explore novel  
19 airway modeling techniques, and that includes 3D  
20 lung airway reconstruction and conducting  
21 computation of fluid dynamic studies in this  
22 geometry. And by doing the 3D reconstruction, we

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1 look for variables that are associated with the  
2 disease.  
3 This could include the bronchial  
4 cross-sectional area, airway partitioning between  
5 healthy and diseased lobes, airway resistant,  
6 impedance, and other parameters.  
7 By doing the computational fluid dynamic  
8 studies, we would like to study drug delivery to  
9 the -- first we would like to study the airflow  
10 distribution, from which we can calculate or we can  
11 estimate the lung function that we need to use as  
12 the biomarker. And then next would be to study  
13 drug delivery to the diseased lung.  
14 This step actually is pretty extensive and  
15 needs an expert of people in the field to do it.  
16 However, it would be desirable to have this package  
17 in a simpler way, like a multiple-path dosimetry  
18 model that allows clinicians and other health  
19 professionals to run the model for the specific  
20 patient on desktop computers.  
21 This model I'm talking about is a 1D  
22 representation of the whole 3D modeling. It's been

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1 simplified so it can run fast with fairly good  
2 accuracy, and has already been developed for  
3 healthy lungs. And the next step would be to  
4 include the diseased lung at different stages into  
5 this model.  
6 Some preliminary results have already been  
7 obtained. First, there are 8 CT scan of the lungs  
8 of the kids, children with CF, 4 males, 4 females,  
9 and ages from 3 months to 5 years old. And this  
10 data has been collected as part of an NIH study  
11 with PI Stephanie Davis and co-PI Julia Kimbell.  
12 These are the reconstruction of all these  
13 airways from -- it's a 3 month old girl, 10 months,  
14 12 months and 3-year-old girls, one 3-year-old boy  
15 and three 5-year-old boys. So we did some  
16 preliminary studies on these reconstructions.  
17 The first thing we did was we calculated the  
18 cross-sectional area of the left and right main  
19 bronchi from reconstruction of the airway tree that  
20 went down at least three generations, and then we  
21 expressed it as a percentage of the total  
22 cross-sectional area.



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1 The same we did for the lung ventilation,  
2 calculated it by doing CFD studies assuming steady-  
3 state respiratory flow at resting breathing rate.  
4 We calculated the lung airflow going to the left  
5 and right lobe. And then also we expressed that as  
6 the fraction of the total inhaled airflow.  
7 This is the results. I'm just showing the  
8 sense of it. On the left panel, we have plotted  
9 for each subject the airflow rate and the  
10 cross-sectional area in blue and red bars. And on  
11 the right, you have these two parameters plotted  
12 against each other. So early findings is that it  
13 show that actual the airflow distribution between  
14 left and right lobes are generally similar to the  
15 cross-sectional area between the two main bronchis.  
16 There is also some work ongoing which I'll  
17 touch on that, looking at two 12-month-old CF  
18 subjects. So further work is needed to validate  
19 the accuracy of these reconstructions, and also  
20 look for other variables that might be of interest  
21 to detect the disease.  
22 So these two actually would be very useful,

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1 have the potential to quantify the effect of CF at  
2 early age on lung structure and lung function.  
3 Based on that, we can develop treatment policies.  
4 These are the two 12-month-old subjects I just  
5 mentioned, so subject-1 top, subject-2 bottom.  
6 Left column shows you reconstruction of the lung at  
7 the end of inhalation. The right column shows at  
8 the end of exhalation. And there's a big  
9 difference.  
10 You can see the lung has shrunk at the end  
11 of exhalation. So this is actually to see -- the  
12 reason we see that, on the left the airways are  
13 fully expanded on the inhalation, but they  
14 disappear at the end of exhalation. And this is  
15 because airways have collapsed.  
16 There are additional data available, so  
17 these were just two. There were over 50 scans, CT  
18 scans, of the lungs of 12-month-old children, and  
19 in addition, images are available for healthy kids  
20 from birth to 17 years old from a different R01  
21 study. So this database can basically be the  
22 foundation to study drug delivery to diseased lung

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1 and the dosing in healthy and diseased lung.  
2 The last slide, I have personally noticed  
3 recent interest by the FDA on doing CFD studies.  
4 And what I'm trying to promote is that we probably  
5 should be -- if data is available, should be using  
6 actual scans rather than using idealized geometry,  
7 which I have seen that a lot recently. And this  
8 data are already available.  
9 For this particular case, recommendation is  
10 to use the 3D reconstruction of the CT scans of the  
11 children with disease, and compare that with the  
12 lung reconstruction of children with healthy lungs  
13 for which scans are available, then, to study these  
14 biomarkers. And conduct computational fluid  
15 dynamic studies to study airflow in the lungs of  
16 both healthy and diseased lungs.  
17 Then look for possible ways to maximize  
18 airflow and drug delivery to the lobes that are  
19 affected. As I mentioned, they're hard to get to  
20 normally because the lungs are damaged. And also  
21 minimize the side effects as the results of drug  
22 going to these sites that are not of interest.

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1 Then we would like, as I mentioned earlier,  
2 that we would like to package this is in a  
3 multiple-path dosimetry model to allow clinicians  
4 and health professionals to be able to run this for  
5 a specific patient on desktop computers. And  
6 finally, be able to validate these models by  
7 comparing with experimental measurements. Thank  
8 you.  
9 DR. LIONBERGER: So can you say what would  
10 the impact of this be on the development of generic  
11 drug products?  
12 DR. ASGHARIAN: Well, this actually is the  
13 framework for any drugs, so if that could be -- so  
14 basically, this is a generic model that can be  
15 applied to any scenario, including generic drugs.  
16 So that's the whole idea, that it's not anything  
17 specific.  
18 DR. LIONBERGER: All right. Thanks very  
19 much.  
20 DR. ASGHARIAN: Sure.  
21 DR. LIONBERGER: So move on to our next  
22 speaker. It will be Tracy Rupp from the National

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1 Center for Health Research.  
2 Presentation – Tracy Rupp  
3 DR. RUPP: Good afternoon. Thank you for  
4 the opportunity to speak today. My name is Tracy  
5 Rupp. I am a pharmacist and the director of Public  
6 Health Policy Initiatives at the National Center  
7 for Health Research.  
8 Our research center analyzes medical and  
9 scientific data and provides objective health  
10 information to patients, providers, and  
11 policymakers. We don't accept funding from the  
12 drug or medical device industry, and I have no  
13 other conflicts of interest.  
14 The first policy issue or GDUFA research  
15 issue that I'd like to talk about is the inspection  
16 of manufacturing plants. We've heard today that  
17 patient and prescriber confidence in generics is  
18 disproportionately shaped by the recalls and  
19 quality issues that occur.  
20 So increased attention to manufacturing and  
21 quality control is critical. And importantly, we  
22 have heard how bioequivalency for complex generic

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1 drugs is highly dependent on the quality control of  
2 the manufacturing process.  
3 In 2012 Congress passed the FDA Safety and  
4 Innovation Act, or FDASIA, which among other things  
5 requires the agency to inspect foreign facilities  
6 that make drugs sold in the United States as  
7 frequently as it inspects domestic plants.  
8 In addition to achieving parity in the  
9 frequency of inspections, FDA also committed to  
10 ensuring that domestic and foreign inspections are  
11 conducted with comparable depth and rigor.  
12 A 2015 report from the Office of the  
13 Inspector General found that FDA has made progress  
14 on oversight and inspection of manufacturers of  
15 generic drugs, but gaps remain.  
16 For example, FDA increased its preapproval  
17 inspections by 60 percent between 2011 and 2013.  
18 However, it didn't conduct all of the preapproval  
19 inspections requested by its own generic drug  
20 application reviewers during this time period. And  
21 most unfulfilled requests were for inspections of  
22 foreign manufacturers.

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1 FDA staff attributed the outstanding  
2 preapproval inspections to a lack of resources.  
3 And in addition to improving drug quality and  
4 improving consumer confidence in generics, timely  
5 conduct of preapproval inspections could help  
6 reduce delays in the availability of generic drugs.  
7 In recent years, FDA has sent warning  
8 letters about violations to companies with plants  
9 in foreign countries, such as India and China. The  
10 number of warning letters sent to Chinese and  
11 Indian manufacturers for violations nearly  
12 quadrupled from 2012 to 2015. Most of the warning  
13 letters raised concerns about data integrity.  
14 Many of the observations were for egregious  
15 problems, like altering official documents in front  
16 of an inspector, falsifying dates of quality  
17 control testing, or documenting important  
18 manufacturing data on scrap paper in pencil. And  
19 these are the types of issues that can clearly  
20 impact consumer confidence in generic drugs.  
21 Despite the increased resources from the  
22 GDUFA provisions of FDASIA in 2012, it's difficult

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1 to keep up with the increasing production of drugs  
2 and devices in foreign countries. Imports of drugs  
3 and medical devices from China alone increased by  
4 nearly fivefold from 2007 to 2013.  
5 The 2015 OIG report recommended that FDA use  
6 its inspection resources more efficiently by making  
7 greater use of authority granted by FDASIA to  
8 request records in lieu of, or in advance of, an  
9 inspection. The authority could increase FDA's  
10 capacity for preapproval inspections. Record  
11 reviews could be completed in advance rather than  
12 using up the inspection staff's time during an  
13 onsite inspection. The inspector's time onsite  
14 could be prioritized to address the tasks that must  
15 be conducted in person rather than on reviewing  
16 paperwork.  
17 Two important questions are: Has FDA  
18 implemented this recommendation? And if so, what  
19 impact has it had? Additional related regulatory  
20 science research questions could include: Has this  
21 new authority improved the quality of inspections?  
22 Has it helped FDA hone in on the issues posing the

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1 greatest risk to public health?  
2 Can a more focused onsite review help  
3 improve drug quality and reduce the risk of patient  
4 harm from unsafe drugs? Does this new authority  
5 reduce approval delays? Do more frequent  
6 preapproval inspections result in fewer recalls?  
7 And are problems identified and fixed earlier as a  
8 result?  
9 Another important GDUFA regulatory science  
10 research question is how to improve compliance with  
11 the requirement for manufacturers of generic drugs  
12 to register with the FDA. FDA uses the  
13 registration database to help determine which  
14 facilities to inspect, using its risk-based  
15 approach.  
16 The OIG found that of the 432 generic drug  
17 manufacturers listed on ANDAs approved in 2013,  
18 10 percent didn't match entries in FDA's registry  
19 of generic manufacturers. It's worth noting that  
20 62 percent of the manufacturers that couldn't be  
21 located in the registry were foreign.  
22 FDA can't inspect facilities if it doesn't

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1 know they exist. So research is needed to  
2 determine what strategies are most effective for  
3 ensuring registration, including incentives for  
4 registering and effective penalties for those that  
5 don't.  
6 Another important regulatory science  
7 question is the effect of generic drug labeling  
8 updates on patient safety. FDA has issued a  
9 proposed rule that would allow manufacturers of  
10 generic drugs to update their label with new  
11 information as it becomes available. And we  
12 strongly support that rule.  
13 Currently, generic manufacturers have little  
14 incentive to monitor drug safety, and they aren't  
15 required to update the label with new risk  
16 information. As a result, safety monitoring  
17 basically stops when generics enter the market.  
18 This puts patients at risk, since the FDA  
19 found that the median time from initial approval of  
20 the drug product to the time of making a  
21 safety-related labeling change was 11 years, past  
22 the market exclusivity period for many branded

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1 drugs.  
2 The proposed rule would give generic  
3 manufacturers the authority to initiate safety  
4 labeling changes through the changes being effected  
5 process. And the result will be to give patients  
6 access to the most up-to-date product labeling.  
7 It would be helpful if the FDA could conduct  
8 or support research to determine the impact of the  
9 current situation, where labels for generic drugs  
10 are not updated unless the branded version is  
11 updated. It's especially important to compare the  
12 current situation with previous policies.  
13 For example, prior to the Supreme Court  
14 decision *Pliva v. Mensing* in 2011, generic drug  
15 companies were responsible for updating their  
16 labels. Now that they're not required to update  
17 the labels, an interesting question is how many  
18 labels for generic drugs were updated in the five  
19 years prior to the Supreme Court decision compared  
20 to how many have been updated since.  
21 When and if the proposed rule is implemented  
22 in the future, an important question is how will

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1 this affect the timeliness, accuracy and  
2 completeness of drug safety labeling, and will it  
3 protect patients from harm?  
4 The third and last regulatory science  
5 question I'll mention today is related to patient  
6 copay coupons. Like we heard earlier today, as  
7 drug costs continue to rise, brand name  
8 manufacturers are more likely to use coupons to  
9 entice customers to fill their prescriptions since  
10 coupons defray or eliminate the copay costs.  
11 In 2009, coupons were available for fewer  
12 than 100 prescription medicines, but the number  
13 exceeded 700 by last year, according to a recent  
14 analysis by the Tufts Center for the Study of Drug  
15 Development. These coupons are more common just  
16 prior to generic competitors coming on the market.  
17 The goal is to establish brand loyalty and reduce  
18 the number of patients switching to generic  
19 versions.  
20 As we heard earlier today, a 2013 *New*  
21 *England Journal of Medicine* analysis found that  
22 62 percent of coupons were for brand-name drugs for

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1 which a lower cost option existed.  
2 The important regulatory science questions  
3 related to copay coupons include: How do coupons  
4 affect prescribing of generic drugs? What impact  
5 do coupons have on patient outcomes, such as  
6 adherence to therapy and treatment success? And  
7 what is the impact on cost for patients for  
8 Medicare and private insurers?  
9 In summary, generic drug research and  
10 policies have an enormous impact on the health and  
11 safety of millions of Americans, and impact patient  
12 and prescriber confidence in generic drugs. We  
13 urge you to consider research that will improve  
14 drug quality through rigorous manufacturer  
15 inspections, increase patient safety through the  
16 communication of important drug information on  
17 generic drug labels, and promote the uptake of  
18 generic drugs where they have the potential to  
19 reduce cost and improve outcomes.  
20 Thank you for the opportunity to share our  
21 recommendations today, and I'll be happy to take  
22 any questions.

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1 DR. LIONBERGER: Thank you.  
2 DR. UHL: When you mentioned aspects of the  
3 inspections, and you talked about incentives for  
4 registration, do you have any other  
5 thoughts -- could you expand a bit on that? What  
6 would that look like? What are you guys thinking  
7 related to incentives?  
8 DR. RUPP: I guess we haven't --  
9 DR. UHL: What would be required in order to  
10 do that?  
11 DR. RUPP: Right, right. We haven't  
12 specifically come up with any real great ideas.  
13 But we do feel like it may actually end up more in  
14 the realm of being some sort of a penalty being the  
15 incentive. But I think that there could be some  
16 further discussion between industry and the FDA and  
17 other groups, really, to what would be the best way  
18 to approach that.  
19 DR. LIONBERGER: Well, thank you very much.  
20 DR. RUPP: Thank you.  
21 DR. LIONBERGER: So our next speaker is  
22 Professor James Brasseur from the University of

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1 Colorado.  
2 Presentation – James Brasseur  
3 DR. BRASSEUR: Thank you very much. Just a  
4 quick background on myself since I'm rather unusual  
5 in this group. I was at Penn State University for  
6 27 years. One of my primary areas of research was  
7 the interplay between the physiology and the  
8 mechanics of the gastrointestinal tract,  
9 particularly the fluid dynamics areas, because  
10 that's my primary area of expertise.  
11 About 15 years ago, I began working with  
12 pharmaceuticals, first with Janssen Pharmaceuticals  
13 and then with AstraZeneca. I have a long  
14 relationship with Bertil Abrahamsson and his  
15 colleagues at AstraZeneca in Sweden. And about  
16 two, three years ago, I began working with the  
17 University of Michigan, and I'm part of the  
18 FDA-funded program that Gordon Amidon and Duxin Sun  
19 discussed this morning. And this project that I'm  
20 discussing right now is in relationship to that  
21 program of research.  
22 The focus of my discussion and my

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1 recommendations are the improvement in our  
2 understanding of the hydrodynamic effects on  
3 dissolution in the gastrointestinal tract, and  
4 in vitro and its effects on the absorption. and  
5 details associated with modeling such as PBPK type  
6 of approaches, and more complex types of models.  
7 Obviously, the gastrointestinal tract  
8 functions very differently from an in vitro device.  
9 There's transport and mixing, which are both  
10 required in order to deliver any molecule to the  
11 surface, the epithelial surface. That would  
12 include nutrients as well as drug molecules. And  
13 this is a combination of different kinds of  
14 motility events that take place within the  
15 gastrointestinal tract.  
16 It doesn't take much to notice, of course,  
17 that an in vitro device doesn't represent even  
18 approximately these, but that in itself isn't  
19 necessarily indicating that there's a lack of  
20 correspondence between the in vitro and the in vivo  
21 situation. And that's something I would like to  
22 get into.

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1 The primary motility events that take place  
2 in the GI tract are peristaltic or propagating  
3 wave-type contractions and segmental contractions.  
4 These are in the fed state. In the fasting state,  
5 the MMC contraction event is primarily a  
6 propagating type of event, but there are smaller,  
7 different types of contractile events, very  
8 powerful, in MMC3 and so on that are very different  
9 in that the volumes in which the dissolution  
10 process is taking place are much smaller than in  
11 the fed state. So there's very fundamental  
12 differences in the hydrodynamics associated with  
13 differences between the fed and the fasting state.  
14 Obviously, the flow field, the velocity  
15 fields and so on, are very different than they  
16 would be in an in vitro device, and they're very  
17 different from each other in the different types of  
18 contractile events. And those are issues that  
19 we're trying to investigate and that we feel needs  
20 more work.  
21 In particular, if one were to plot, as I'm  
22 showing here -- this is taken from rat data from

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1 and NSF funded program some years ago. And this is  
2 a peristaltic contractile event where the diameter  
3 is plotted as a contour plot, as a function of  
4 time. And these propagating events appear as these  
5 striped contraction reaches. Whereas in a  
6 segmental contraction, you get this checkerboard  
7 kind of a behavior which is consistent with this  
8 picture on the left.  
9 You can imagine that the mixing process, the  
10 release of drug from particles that might be  
11 contained within these segments and so on, will be  
12 very different. And in fact, they are, and we aim  
13 to quantify that using computational fluid  
14 dynamics-type of approaches.  
15 So here's an example of a model that we just  
16 completed developing, and we're now in the process  
17 of using, to create computational experiments in  
18 coordination with the in vivo analyses, the in vivo  
19 experimental dynamics that are being measured at  
20 University of Michigan.  
21 All right. So what I'm showing here are  
22 500 pharmaceutical particles being moved around in

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1 a simulated clean peristaltic wave. This computer  
2 is slower than it should be, so it's not moving  
3 continuously. But at any rate, these particles are  
4 releasing drugs. This is a realistic simulation  
5 for ibuprofen. The release rate is consistent with  
6 the in vivo situation. This is the fed state.  
7 The main message to take away is that these  
8 kinds of simulations can give a lot of detail that  
9 are not available in the in vivo measurements, in  
10 the in vitro measurements, and certainly not in the  
11 standard PBPK type modeling. And in particular,  
12 you notice a lot of heterogeneity.  
13 The uptake at the wall depends in time on  
14 this heterogeneity. The details of the  
15 heterogeneity depend on the motility and other  
16 characteristics of the gastrointestinal tract  
17 versus in vitro.  
18 All right. The modeling has to correspond  
19 with this improved understanding. And one of the  
20 areas in which I have focused in a couple recent  
21 papers is the importance of modeling from a  
22 physics-based type modeling strategy. Models tend

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1 to be empirically based, and I argue that the core  
2 of models should be, as much as possible, connected  
3 to the laws of mechanics. And in particular, this  
4 representation that I'm showing here is an attempt  
5 to do that, where this object here, which has this  
6 symbol "Sh" and stands for what's called a Sherwood  
7 number, has the physics embedded in it. And this  
8 is where the true modeling part lies.  
9 But the solubility difference with what's  
10 called the bulk concentration is another central  
11 parameter, as well as the radius. And this has  
12 come up several times in yesterday and today's  
13 meetings. But it's this parameter in which the  
14 hydrodynamics is embedded.  
15 So one can write this expression as a first  
16 term, which is a pure diffusion model in an  
17 infinite domain, sink conditions. The second term  
18 is a correction for those sink conditions. And the  
19 third term is the hydrodynamics. And this has two  
20 effects. One is shear -- or, sorry, one is  
21 convection. This is the standard one. And one is  
22 shear, which is a new one that we've found in our

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1 work to be more important than convection.  
2 So what are the mechanisms by which one can  
3 compare in vitro and in vivo? And again, it's  
4 obvious that the global flow is totally different.  
5 But that doesn't necessarily mean that the in vitro  
6 device is not relevant to the in vivo.  
7 What matters is the release of drug from  
8 individual particles, thousands of these, that are  
9 moving through the device. And if the rate of  
10 release of drug is consistent with the in vivo  
11 scenario, then it's in vivo relevant.  
12 The parameters that are required to describe  
13 this process of drug release are local, local to  
14 the particles of the drugs themselves. And these  
15 are fluid dynamics parameters that people in the  
16 fluid dynamics community understand. This one is  
17 called a Reynolds number. This one is called a  
18 Peclet number. But the point is that these are  
19 local to the particle.  
20 For example, one needs to estimate the  
21 relative speed between the particle and the flow to  
22 determine these Reynolds numbers or these numbers

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1 that determine the rate of release of drug from the  
2 particle surface. And this is what is meant by  
3 hydrodynamic effect.  
4 It turns out that there's another  
5 hydrodynamic effect that we discovered a couple  
6 years ago, and that's related not just to the  
7 relative speed between the particle and the flow,  
8 but to something called the shear rate. This is  
9 something in the fluid mechanics of the flow  
10 itself.  
11 But the main point is that it's very  
12 different in this kind of a device than it is in  
13 the in vivo situation. And this is a  
14 characteristic that makes the in vivo situation  
15 different from the in vitro situation.  
16 So these are computer simulations, for  
17 example, from the literature of a USP-2 device  
18 where this parameter that I call shear rate is up  
19 at around 100 maximum, whereas we've done  
20 simulations in our gut model, and their maximum to  
21 2, 3, 4, 5 inverse seconds. So two orders of  
22 magnitude difference. And this is the main

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1 difference between the in vivo and the in vitro  
2 situation, not the global flow itself.  
3 So these numbers, if you compare the  
4 intestines with USP 2 device, are very different,  
5 orders of magnitude different. But they're also --  
6 this number is very different from this number, and  
7 that's another issue. So for example, if one  
8 actually does -- and so we did a large series of  
9 calculations to show this Sherwood number, which is  
10 a nondimensional release rate for the drug, as it  
11 were.  
12 So this is the number that characterizes the  
13 hydrodynamic effect. One means no hydrodynamic  
14 effect. Numbers bigger than 1, so this is twice  
15 the non-hydrodynamic release rate, 3 times, 4  
16 times.  
17 What we're plotting here is against this  
18 thing that I called Peclet number. But the details  
19 aren't important. Important is that this shows  
20 that there is a large variation. depending on this  
21 number. And when you compare the in vitro with the  
22 in vivo, they're very different, so that the in

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1 vitro situation is releasing drug at three, four  
2 times the rate of the in vivo situation. But even  
3 in the in vivo situation, there's a broad range  
4 that has hydrodynamic effects involved in it.  
5 So we need to understand this better. We  
6 need to include this into the modeling. It hasn't,  
7 to date, been included in the modeling. Of course,  
8 the beauty about computer simulation is you can  
9 answer the question why. Why is there enhancement?  
10 I don't have time to go into it, but in a nutshell,  
11 it's because the particles spin because of these  
12 effects, and the spinning creates a local  
13 enhancement of the release rate.  
14 This has been validated through in vitro  
15 experiments that we did together as a group at the  
16 University of Michigan. Greg Amidon and Deanna  
17 Mudie worked with me and my team. And these were  
18 well-validated.  
19 This is a computer simulation or  
20 mathematical model simulation compared against the  
21 data, and we validated it. It works very well.  
22 And not only does it work well, but it turns out

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1 it's in vivo- and in vitro-relevant. It's  
2 important. We've now validated that.  
3 This is the last slide, which shows -- this  
4 is the standard way in which modeling is typically  
5 done in the PBPK world. And it's done using what's  
6 called a diffusion layer thickness model. And my  
7 argument is that this diffusion layer thickness  
8 model is ad hoc and it needs to be based on first  
9 principles.  
10 In this case, we're basing it on the shear  
11 effect. And you can see that the curves, which are  
12 often represented in this form, depend on the shear  
13 rate, and the shear rate depends on the flow, the  
14 flow depends on in vitro versus in vivo, and also  
15 depends on the particle where it happens to be  
16 sitting at any given point in time.  
17 So my take-home message is that the  
18 hydrodynamic influences are important to study.  
19 There's very little that's understood about them,  
20 and so there needs to be a lot more. But also, the  
21 modeling needs to be put on a more first principles  
22 basis, bases that are based on the conservation

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1 principles, what are called the laws of mechanics  
2 or the laws of physics, at the core. And I think  
3 there needs to be a movement to try to move some of  
4 these models to a more physical core.  
5 Obviously I can only say so much in  
6 10 minutes. There's all sorts of sub-issues that  
7 perhaps will come up in the questions right now.  
8 Thank you.  
9 DR. LIONBERGER: All right. Thanks very  
10 much. As a chemical engineer who has taught  
11 graduate fluid mechanics, it made perfect sense to  
12 me.  
13 (Laughter.)  
14 DR. BRASSEUR: Excellent. Excellent.  
15 DR. LIONBERGER: But it's a question, right,  
16 to identify. You know the question we're looking  
17 at here is what should we, as we're preparing a  
18 regulatory science research program, look at next  
19 to advance this area?  
20 Should we be looking at the in vitro  
21 dissolution apparatus to make them more like the  
22 physiological situation? Do we need more data on

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1 the in vivo physiology to confirm this? So what  
2 would be the next sort of research --  
3 DR. BRASSEUR: Well, obviously, the emphasis  
4 of my presentation was more on the hydrodynamics  
5 and the modeling aspects. And I feel very strongly  
6 that this cannot be evolved or developed or  
7 improved in isolation of the real situation.  
8 The real situation is that there are  
9 in vitro devices that are designed to measure  
10 dissolution for situations that are in vivo-  
11 relevant. So one of the big questions is, to what  
12 extent are they, and to what extent is that  
13 important? So these need to be integrated, and I  
14 already gave you one example of where we have done  
15 that.  
16 But it also needs to be integrated with the  
17 in vivo scenario. And the in vivo scenario is a  
18 rather different one. You can do certain things  
19 with modeling and on the computer that you can't do  
20 in vivo and vice versa.  
21 So the real challenge is to integrate them  
22 in a way that advances our knowledge and our

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1 modeling capabilities, and that's of course what  
2 we're trying to do at the University of Michigan  
3 with me and my team. And I think there needs to be  
4 more of that kind of integration done.  
5 DR. LIONBERGER: Thanks very much. So our  
6 final speaker is Professor Jim Polli from the  
7 University of Maryland.  
8 Presentation – Jim Polli  
9 DR. POLLI: Okay. I apologize, I do not  
10 have any good videos. So a lot of people have  
11 already mentioned, talked about excipients, so I'll  
12 try to just be brief. My major comment is it would  
13 probably be good to do more excipient-based  
14 research.  
15 As the group knows, drug product quality is  
16 a major focus. There's a need over the lifespan of  
17 products to make sure their quality is assured,  
18 both before generics and after generics. So  
19 there's always a need for equivalence testing.  
20 So here we have two formulas, one of the  
21 innovator product of lamotrigine and one an example  
22 generic of lamotrigine. And it probably would be

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1 very interesting if we were to take a survey of  
2 various folks -- healthcare providers,  
3 pharmaceutical scientists, what have you -- when  
4 they look at this, what is it that they see? What  
5 sort of risks do they see? And I would suggest  
6 that there's huge differences in points of view  
7 among various stakeholders in how they would  
8 describe similarity or differences between these  
9 two formulations.

10 But arguably, a major area where differences  
11 can occur are excipients. And then we can ask the  
12 same question: Well, is there a difference between  
13 lactose and lactose monohydrate in the context of  
14 ongoing drug product quality?

15 To some extent that's been answered, but to  
16 a fair extent it hasn't. And I think this  
17 uncertainty has persisted for a long time, and it  
18 would be helpful from a biopharmaceutic standpoint  
19 to have better-developed literature around  
20 excipients, or at least the most common excipients.

21 So as everyone knows, there are biowaivers.  
22 There are all sorts of different types of

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1 biowaivers, including so called Biopharmaceutics  
2 Classification System-based biowaivers where the  
3 focus is on applying biowaivers using in vitro  
4 testing, et cetera, to so-called less risky drugs.  
5 But then the question is, which are those? And  
6 within the last year, the FDA put out a guidance  
7 that expanded the BCS to include so-called  
8 Class III drugs, drugs with high solubility and low  
9 permeability.

10 This is from an article from the FDA from a  
11 couple years ago illustrating the distribution in  
12 ANDAs with regard to BCS Class I, II, III and IV.  
13 And Class I and III make up a large part of drugs  
14 that are in ANDA applications. So it seems as if  
15 expansion of the BCS will have a fair impact.

16 Of course, the concern with excipients in  
17 the context of biowaivers are, to the excipients,  
18 are they in fact not doing anything that's bad in  
19 terms of drug absorption or any other types of  
20 issues? And the things that come to mind are  
21 gastrointestinal transit, dissolution, stability,  
22 interacting with transporter metabolism, that sort

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1 of thing.

2 It would be very easy to point to certain  
3 things on here where there's very little studies.  
4 There's probably not much study with regard to  
5 excipients and transporters or excipients and  
6 metabolism. So in some ways these excipients,  
7 these common excipients, are very familiar, but in  
8 other ways they're actually very poorly studied.

9 So earlier this year, working with the FDA,  
10 we published this article -- this was back in  
11 January -- "Lack of in vivo impact of common  
12 excipients on oral drug absorption of BCS Class III  
13 drugs, cimetidine and acyclovir." So these were  
14 two model BCS Class III drugs.

15 They were subjected to two studies -- I'm  
16 going to very briefly describe them -- where the  
17 goal was to examine 14 common excipients. There  
18 was three capsule formulations for each drug  
19 cimetidine and acyclovir, where large quantities of  
20 excipients were in each of the various  
21 formulations.

22 Each drug was subjected to a fasted single-

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1 dose 4-way crossover study in healthy volunteers.  
2 There's an oral reference. And average BE was  
3 employed to assess impact of excipients. Here's  
4 the design of what I just talked about. And  
5 towards the bottom there, you can see there were  
6 three test capsules of cimetidine and three test  
7 capsules of acyclovir, each having large quantities  
8 of excipients collectively across 14 common  
9 excipients.

10 In study 2, there was follow-up with  
11 cimetidine, HPMC, and magnesium stearate. And the  
12 first study probably slowed down dissolution a  
13 little bit, with was not the interest. The  
14 interest was actually not so much a dissolution  
15 study but more looking at whether excipients have  
16 an impact on permeability or transit, that sort of  
17 thing.

18 So in study 2, HPMC and magnesium stearate  
19 were reduced. Okay? And then collectively across  
20 the series of studies, we were able to  
21 identify -- 12-of the excipients had no impact on  
22 bioavailability. And you can see, or maybe you



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1 can't, but in the second column after the listing  
2 of the excipient, you can see that very large  
3 quantities of these common excipients were studied.  
4 The first two, microcrystalline cellulose  
5 and HPMC, actually failed Cmax, so we weren't able  
6 to say anything different than what's currently in  
7 the guidance with regard to qualitatively the same  
8 and quantitatively very similar. But overall, we  
9 think there was a lot of regulatory relief that  
10 could be found in this type of data.  
11 So the conclusions were, 12 of the 14 were  
12 found to be non-problematic, and such that those  
13 excipients could be employed in Class III  
14 biowaivers such that they're not more than those  
15 that were studied here in this particular sequence  
16 of studies.  
17 Again, HPMC and microcrystalline cellulose,  
18 because of the Cmax, with one particular  
19 formulation should be qualitatively the same and  
20 quantitatively very similar to the reference.  
21 We do say in the paper some caveats. It's  
22 possible that other drugs might be different than

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1 these two particular ones, so there needs to be at  
2 least some level of caution. And then we also say  
3 the greatest concern would appear to be a drug that  
4 depends on an uptake transporter such that the  
5 excipient could possibly inhibit, by virtue of the  
6 excipient having the same molecular structure,  
7 similarity to the transporter's pharmacophore  
8 recognition site.  
9 Then soon after that was published, there  
10 was actually -- some pharmacokineticist challenged  
11 the -- not so much the data, but just the  
12 interpretation. So this is where I'm going.  
13 There's probably a need to have some sort of a way  
14 forward to agree on what the biopharmaceutical  
15 implications of certain excipients are.  
16 I think this is actually a quote from their  
17 letter. "Results obtained in our study should not  
18 be extrapolated to other drugs." They're  
19 suggesting that, oh, that's all great for those 2  
20 drugs, acyclovir and cimetidine, but it shouldn't  
21 be extrapolated to any other Class III drugs. And  
22 then there's the reference there for our particular

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1 reply. And I do have to say, I think they raise a  
2 good point about just generalizability.  
3 So to summarize, like many of the other  
4 speakers, I think there's a need for greater  
5 research in excipients. In some ways, they're very  
6 familiar but I think in other ways, in critical  
7 ways, they're actually -- there's a lack of data  
8 underpinning certain decisions that could be made  
9 that would benefit development.  
10 There was also a presentation earlier today  
11 about pediatric applications. And as you know,  
12 that's a big area. There's been a lot of  
13 improvement in the last 10-years. There's perhaps  
14 been a doubling of labels, of drug labels. But I  
15 still think probably not much has been broadly  
16 generalized with regard to excipient use in  
17 children.  
18 I recall some of the questions this morning  
19 about some of the excipient talks. And I guess one  
20 suggestion would be -- I'm thinking about some of  
21 the BCS biowaivers that are published in the  
22 Journal of Pharmaceutical Sciences, and those are

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1 extremely well-received. They're extremely highly  
2 referenced and downloaded.  
3 Maybe the same sort of thing for the  
4 excipient side -- it would be very nice to have  
5 monographs of excipients with regard to at least  
6 biopharmaceutical aspects. A lot of chemistry  
7 aspects are well-known with regard to excipients,  
8 but with regard to some of these questions about  
9 ongoing drug quality, it's the biopharm side that  
10 seems to be a little less tied down. Thank you  
11 very much.  
12 DR. LIONBERGER: Thanks very much.  
13 Questions?  
14 So is there a sense that the issue with  
15 excipients -- and you mentioned specifically -- is  
16 it really specifically interactions with  
17 transporters and enzymes? Or do we think there's  
18 other mechanisms by which they have biopharmaceutic  
19 effects?  
20 DR. POLLI: My own personal opinion, I think  
21 that the most common excipients are used incredibly  
22 frequently, right, and in a variety of different

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1 formulations where there's a variety of different  
2 processing. And I think in -- for example, let's  
3 just take lactose. Lactose is used in very large  
4 quantities in many products.  
5 But having said that, this opinion here,  
6 results should not be extrapolated to other drugs.  
7 One could put together an argument that the levels  
8 of lactose have not been well studied with regard  
9 to bioequivalence and that sort of thing.  
10 So it really is a matter of opinion, I  
11 think. There's not one source that summarizes,  
12 here's everything that we know about a particular  
13 excipient. Everyone probably knows the handbook,  
14 but that excipient handbook probably has nothing in  
15 it with regard to biopharmaceutic elements that  
16 often come into play. So I think a lot of things  
17 have to do with what paper you might be familiar  
18 with and how familiar are you with that particular  
19 excipient, that sort of thing.  
20 DR. UHL: So your basic premise was that  
21 there's a need for more excipient research?  
22 DR. POLLI: Yes. Well, maybe just a

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1 collating of what's already out there. And there's  
2 been a lot of right progress in the last year with  
3 regards to the inactive ingredient database. So  
4 maybe more of that sort of thing, what's already  
5 available.  
6 What's the counter argument to someone  
7 saying, you can't generalize it to another drug?  
8 And you can go through the process that Dr.  
9 Lionberger was outlining in terms of, well, it  
10 could be this aspect. Could be transit. It could  
11 be some sort of metabolism concern. It could be  
12 some sort of transporter concern. But then you can  
13 ask the question -- I can tell you, there's not  
14 many articles that study excipient effects on  
15 metabolism.  
16 So it's very easy to say there's not much  
17 you can hang your hat on. Having said that, these  
18 common excipients are used extensively. So it does  
19 come -- it often comes down to a matter of opinion  
20 ,I think.  
21 DR. LIONBERGER: Thanks very much.  
22 Question? All right.

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1 So that concludes the formal program.  
2 Before I turn it over to Cook for closing remarks,  
3 I want to thank some of the people who did all the  
4 work to organize this meeting.  
5 So that would especially be, if you were  
6 involved in the meeting at all, Thushi Amini and  
7 Jessica Alfaro, who are your contacts to set up the  
8 scheduling. Got the room. Got the logistics  
9 everywhere.  
10 I know that Thushi's been responsible for  
11 this for the last four years and really been  
12 handing it off and training the apprentice. So I  
13 feel we just have to show up here and everything  
14 works. That's just a sign of excellence.  
15 I also want to thank a lot of other staff  
16 from my office, Office of Research and Standards,  
17 especially Krista Andre, who has been working on  
18 the slides there, as well as all the staff from our  
19 office -- the scientists who are doing this were  
20 also the people who were checking you in. It's a  
21 great privilege to work here. I know that people  
22 in our office work very hard, willing to do

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1 anything it takes to get this meeting successful.  
2 The work that I talked about this morning,  
3 there are people from our office involved with all  
4 of these external collaborations, making sure that  
5 they're running well, that they're meeting the  
6 needs of the generic drug program.  
7 So there's a huge of amount of effort by a  
8 large number of staff that makes all of those  
9 activities that we're doing possible. And I just  
10 want to recognize them and thank them for all their  
11 efforts in making this meeting successful. So  
12 thank you very much.  
13 (Applause.)  
14 DR. LIONBERGER: So now our office director  
15 will make some closing remarks.  
16 DR. UHL: Okay. So I get the dubious  
17 distinction of being the one that gets the last  
18 word in, although the words are given to me, thank  
19 you very much, by Thushi. So on behalf --  
20 DR. LIONBERGER: She took off.  
21 Closing Remarks  
22 DR. UHL: That's okay. Needless to say, I

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1 have augmented and ad libbed a couple things here,  
2 so she's a little scared, I'm sure.  
3 So on behalf of the FDA panel, I'd like to  
4 especially express my appreciation to the  
5 presenters today, and to everyone in the audience,  
6 whether you're attending in person or whether you  
7 are by webcast. And I don't think we have an exact  
8 number of how many are by webcast, but those of you  
9 out there, we're very appreciative of your interest  
10 in this topic and for your attention to the  
11 presentations discussed at today's meeting.  
12 I'd also like to thank the panel members.  
13 Everybody sitting up here has more than enough work  
14 to do in their day job, and it's a Herculean feat,  
15 I think, to get -- what do we have up here -- 12  
16 FDA leaders basically agreeing to sit here, listen  
17 to these presentations, engage with the presenters,  
18 and ask provocative questions so that Rob and his  
19 staff can work with all of the offices to create a  
20 very robust regulatory science program for GDUFA.  
21 So to all of you sitting up here, I thank you very  
22 much.

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1 I also want to echo some of Rob's thanks.  
2 I'd especially like to thank Jessica for all her  
3 hard work, and for making this public hearing run  
4 smoothly today. I want to thank Thushi for  
5 actually delegating and training Jessica.  
6 So for those of you who have attended the  
7 last three years, Thushi usually has massive  
8 insomnia by this time, making sure that this  
9 meeting runs as smoothly as it does. And I have  
10 coached her extensively to delegate, so I am  
11 thrilled to see that she has. And Jessica, I thank  
12 you for letting her train you. So thank you very  
13 much.  
14 I'd also like to thank all of Rob's staff.  
15 All of the staff in the Office of Research  
16 Standards at OGD are so engaged in this meeting and  
17 are -- really want to be sure that this runs  
18 smoothly. And I think, for those of you who are  
19 not with the agency, what Rob said is true. Our  
20 scientists are the ones out there greeting you.  
21 This is not just standard admin support. I  
22 mean these are the workers behind the scene that

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1 provide you with what Rob showed, a pretty  
2 incredible return on investment of this program.  
3 If I was looking at my financial portfolio and saw  
4 a company with that kind of ROI, if I was allowed  
5 to invest in it, given the ethics standards here at  
6 the agency, I would wholeheartedly.  
7 So to all of them, I thank them for making  
8 not just today run well, but for the success of  
9 this program. And I thank Rob for his leadership  
10 of this program.  
11 Anyhow, for the Generic Drug Products, the  
12 GDUFA Regulatory Science Program is a platform that  
13 allows for collaboration between the FDA and our  
14 external stakeholders in order to develop generic  
15 drugs, and to find and establish new tools and  
16 methodologies that could be used in generic drug  
17 development and regulation.  
18 As with our previous Part 15 hearings, this  
19 hearing was extremely productive and informative.  
20 FDA and OGD will carefully consider all the  
21 comments, both today physically at this meeting and  
22 as well from the submissions to the docket, as we

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1 develop the fiscal year 2017 regulatory science  
2 initiatives under GDUFA.  
3 Once approved by the CDER center director,  
4 Dr. Janet Woodcock, the priorities list will be  
5 posted on the GDUFA regulatory science webpage. So  
6 it will be publicly available.  
7 The docket will remain open until June 17th,  
8 so you have a little bit less than a month to still  
9 get any comments in. We strongly encourage all  
10 interested parties, so those attending in person,  
11 or those by webcast, or people that you know who  
12 may have an interest in this field who weren't able  
13 to attend, we ask you to please provide that  
14 information so that they can comment to the docket.  
15 It is your external input into this program that is  
16 making this program as robust as it is.  
17 We also ask, from any of the presenters, if  
18 you have additional comments, if you can please as  
19 well send them to the docket, and ask you if you  
20 can elaborate on any of your recommendations. So I  
21 know there were questions posed that were different  
22 from what were in your slides, so please.

1 If anyone needs any further details about  
2 that, I ask that you please refer to the Federal  
3 Register Notice. Or, if you don't know where that  
4 is or how to find it, Jessica and Thushi can direct  
5 you to that.

6 So with that said, I thank everyone very  
7 much for your participation. I hope you have a  
8 nice, albeit rainy, weekend. And I would say that  
9 the final is that today's meeting is now concluded.

10 So thank you.

11 (Applause.)

12 (Whereupon, at 4:15 p.m., the meeting was  
13 adjourned.)

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	325:15 <b>12:02 (1)</b> 160:17 <b>12-month-old (3)</b> 285:17;286:4,18 <b>12-of (1)</b> 316:21 <b>13 (3)</b> 30:19;31:1;58:4 <b>14 (5)</b> 173:17;189:9;315:17; 316:8;317:11 <b>15 (14)</b> 1:7;10:10,11;14:15; 80:6;81:22;137:1;152:3; 226:9;249:11;255:19; 258:7;299:11;327:18 <b>1500 (1)</b> 24:17 <b>1503 (1)</b> 1:20 <b>15-minute (3)</b> 11:13,14;279:19 <b>16th (1)</b> 137:2 <b>17 (1)</b> 286:20 <b>17th (2)</b> 16:17;328:7 <b>18 (1)</b> 62:20 <b>19 (1)</b> 13:22 <b>1990 (1)</b> 77:22 <b>1D (1)</b> 283:21	290:17;295:14 <b>2012 (7)</b> 1:3;10:11;34:1; 216:15;290:3;291:12,22 <b>2013 (4)</b> 290:17;292:4;293:17; 296:20 <b>2015 (3)</b> 290:12;291:12;292:5 <b>2016 (5)</b> 1:5,11;18:2;34:3; 266:19 <b>2017 (4)</b> 11:4;220:10;223:3; 328:1 <b>20-person (1)</b> 37:1 <b>21 (3)</b> 254:11,21,22 <b>21st (2)</b> 84:11;85:6 <b>232 (1)</b> 221:5 <b>24-hour (1)</b> 252:5 <b>25 (2)</b> 77:15,16 <b>27 (1)</b> 299:6 <b>2-year-old (1)</b> 115:14 <b>2-year-olds (1)</b> 125:18	119:4 <b>3-year- (1)</b> 125:20 <b>3-year-old (3)</b> 120:1;284:14,14 <b>4</b> <b>4 (11)</b> 206:15,16;207:7; 209:11,11;210:2; 252:13;284:8,8;306:21; 307:15 <b>4/3 (1)</b> 209:12 <b>4:15 (2)</b> 1:12;329:12 <b>4:30 (1)</b> 11:12 <b>40 (4)</b> 37:20;181:8;199:7; 273:5 <b>41 (1)</b> 255:16 <b>432 (1)</b> 293:16 <b>45 (1)</b> 215:13 <b>4-hour (1)</b> 252:6 <b>4th (1)</b> 137:20 <b>4-way (1)</b> 316:1 <b>5</b> <b>5 (6)</b> 220:14;223:10;267:3, 13;284:9;306:21 <b>50 (9)</b> 22:1;81:22;94:9; 99:17;135:20,21;252:11, 12;286:17 <b>500 (1)</b> 302:22 <b>501c3 (1)</b> 136:22 <b>505b2 (1)</b> 266:3 <b>5-year-old (2)</b> 120:2;284:15 <b>6</b> <b>6 (4)</b> 37:14;97:7;221:15; 267:3 <b>60 (3)</b> 82:4;93:1;290:17 <b>62 (2)</b> 293:20;296:22 <b>6-week (1)</b>	97:7 <b>7</b> <b>7 (7)</b> 93:14;94:6;168:21; 229:12,17,18,22 <b>70 (1)</b> 81:16 <b>700 (1)</b> 296:13 <b>75 (2)</b> 252:11,11 <b>8</b> <b>8 (1)</b> 284:7 <b>80 (2)</b> 81:16;264:20 <b>85 (1)</b> 253:14 <b>86 (1)</b> 253:12 <b>88 (1)</b> 20:20 <b>88-percent (2)</b> 226:1,7 <b>9</b> <b>9 (2)</b> 163:20;256:21 <b>9:00 (2)</b> 10:2;108:7 <b>9:04 (1)</b> 1:12 <b>90 (8)</b> 22:2;181:8;215:17; 252:9,10,10,11;262:2 <b>900 (2)</b> 81:10;110:22 <b>95 (3)</b> 139:1;250:8;256:21 <b>97 (1)</b> 139:1 <b>A</b> <b>Aaron (1)</b> 63:11 <b>AbbVie (1)</b> 87:9 <b>ability (5)</b> 33:1;85:10;203:1; 222:17;224:16 <b>able (52)</b> 11:9;16:7;18:20; 23:20;27:11;28:12,17; 34:13,14,16,19;39:4; 60:13;65:2;122:21; 134:16;168:7;175:2,8, 21;179:7,11;187:5,11;
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