

*GDUFA 2012 REGULATORY SCIENCE INITIATIVES
Request for Public Input - FY2018 Generic Drug Research*

May 3, 2017

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

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1 FOOD AND DRUG ADMINISTRATION 2 3 4 Generic Drug User Fee Amendments of 2012 5 Regulatory Science Initiatives: 6 7 Request for Public Input for 8 FY 2018 Generic Drug Research 9 10 Public Workshop 11 12 13 Wednesday, May 3, 2017 14 8:33 a.m. to 4:28 p.m. 15 16 17 18 FDA White Oak Campus 19 10903 New Hampshire Avenue 20 Building 31, Room 1503 21 Silver Spring, Maryland 22	1 Stephanie Choi, PhD (Moderator) 2 Associate Director for Science (Acting) 3 Office of Research and Standards 4 Office of Generic Drugs, CDER 5 6 Badrul Chowdhury, MD, PhD 7 Director 8 Division of Pulmonary, Allergy, and Rheumatology 9 Products 10 Office of Drug Evaluation II 11 Office of New Drugs, CDER 12 13 Dale Conner, PharmD 14 Director 15 Office of Bioequivalence 16 Office of Generic Drugs, CDER 17 18 Denise Cook, MD 19 Senior Medical Officer 20 Division of Dermatology and Dental Products 21 Office of Drug Evaluation III 22 Office of New Drugs, CDER
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1 Meeting Roster 2 Jessie L. S. Au, PharmD, PhD 3 Chief Scientific Officer, Optimum Therapeutics, LLC 4 Founding Director, Institute of Quantitative 5 Systems Pharmacology 6 Research Professor & Mosier Endowed Chair of 7 Pharmaceutical Sciences, University of Oklahoma 8 Chair Professor in Systems Pharmacology, Taipei 9 Medical University 10 Distinguished University Professor Emeritus 11 The Ohio State University 12 13 Diane J. Burgess, PhD 14 Board of Trustees Distinguished Professor of 15 Pharmaceutics 16 University of Connecticut 17 18 Stephen R. Byrn, PhD 19 Charles B. Jordan Professor of Medicinal Chemistry 20 Purdue University, College of Pharmacy 21 22	1 Charlie DiLiberti, MS 2 President 3 Montclair Bioequivalence Services, LLC 4 5 Lanyan (Lucy) Fang, PhD 6 Team Leader 7 Division of Quantitative Methods and Modeling 8 Office of Research and Standards 9 Office of Generic Drugs, CDER 10 11 Joga Gobburu, PhD, MBA 12 Professor of Pharmacy, Practice and Science 13 Director, Center for Translational Medicine 14 University of Maryland, School of Pharmacy 15 16 Stella Grosser, PhD 17 Director 18 Division of Biostatistics VIII 19 Office of Biostatistics 20 Office of Translational Sciences, CDER 21 22

Page 5	<ol style="list-style-type: none"> 1 Ravi S. Harapanhalli, PhD 2 Senior Vice President, Global Regulatory Affairs 3 Amneal Pharmaceuticals, LLC 4 5 Guenther Hochhaus, PhD 6 Professor of Pharmaceutics 7 University of Florida 8 9 Xiaohui (Jeff) Jiang, PhD 10 Deputy Director 11 Division of Therapeutic Performance 12 Office of Research and Standards 13 Office of Generic Drugs, CDER 14 15 David Keire, PhD 16 Director 17 Division of Pharmaceutical Analysis 18 Office of Testing and Research 19 Office of Pharmaceutical Quality, CDER 20 21 22 	Page 7	<ol style="list-style-type: none"> 1 Markham C. Luke, MD, PhD 2 Director 3 Division of Therapeutic Performance 4 Office of Research and Standards 5 Office of Generic Drugs, CDER 6 7 Mehul Mehta, PhD 8 Director 9 Division of Clinical Pharmacology I 10 Office of Clinical Pharmacology 11 Office of Translational Sciences, CDER 12 13 Amitava Mitra, PhD 14 Associate Director, Clinical Development 15 Sandoz, Inc. 16 17 CDR Josephine Nguyen, MD, MS, FAAD 18 Robert Wood Johnson Health Policy Fellow 2016-2017 19 Chairman Kevin Brady's office (TX-8) 20 Assistant Professor of Dermatology 21 US Navy, Uniformed Services University of the 22 Health Sciences
Page 6	<ol style="list-style-type: none"> 1 Myong-Jin Kim, PharmD 2 Deputy Director 3 Division of Quantitative Methods and Modeling 4 Office of Research and Standards 5 Office of Generic Drugs, CDER 6 7 Darby Kozak, PhD 8 Chemist 9 Division of Therapeutic Performance 10 Office of Research and Standards 11 Office of Generic Drugs, CDER 12 13 Sau (Larry) Lee, PhD 14 Deputy Director (Acting) 15 Office of Testing and Research 16 Office of Pharmaceutical Quality, CDER 17 18 Robert Lionberger, PhD 19 Director 20 Office of Research and Standards 21 Office of Generic Drugs, CDER 22 	Page 8	<ol style="list-style-type: none"> 1 John Peters, MD 2 Deputy Director 3 Office of Generic Drugs, CDER 4 5 James Polli, PhD 6 Professor and Ralph F. Shangraw 7 Endowed Chair in Industrial Pharmacy & 8 Pharmaceutics 9 University of Maryland, School of Pharmacy 10 11 Sam Raney, PhD 12 Scientific Lead for Topical and Transdermal Drug 13 Products 14 Division of Therapeutic Performance 15 Office of Research and Standards 16 Office of Generic Drugs, CDER 17 18 Andre Raw, PhD 19 Senior Scientific and Policy Advisor (Acting) 20 Office of Lifecycle Drug Products 21 Office of Pharmaceutical Quality, CDER 22

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<p>1 Amy Rosenberg, MD 2 Director 3 Division of Biologics Review and Research III 4 Office of Biotechnology Products 5 Office of Pharmaceutical Quality, CDER 6 7 Stephan Schmidt, PhD 8 Assistant Professor & Associate Director 9 Department of Pharmaceutics 10 University of Florida 11 12 Paul Seo, PhD 13 Director 14 Division of Biopharmaceutics 15 Office of New Drug Products 16 Office of Pharmaceutical Quality, CDER 17 18 Aloka Srinivasan, PhD 19 Vice President, Regulatory Affairs 20 Lupin Pharmaceuticals, Inc. 21 22</p>	<p>1 Siva Vaithiyalingam, PhD 2 Vice President, Regulatory Affairs, North America 3 Cipla USA, Inc. 4 5 Raja Velagapudi, MPharm, PhD 6 Executive Director, PD Clinical Development 7 Sandoz, Inc. 8 Session II: Equivalence of locally-acting products 9 10 Xiaoming Xu, PhD 11 Scientist 12 Division of Product Quality Research 13 Office of Testing and Research 14 Office of Pharmaceutical Quality, CDER 15 16 Sarah Yim, MD 17 Director 18 Division of Clinical Review 19 Office of Bioequivalence 20 Office of Generic Drugs, CDER 21 22</p>
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<p style="text-align: right;">Page 13</p> <p style="text-align: center;">C O N T E N T S</p> <p>1</p> <p>2 AGENDA ITEM PAGE</p> <p>3 Opening Remarks</p> <p>4 Robert Lionberger, PhD 15</p> <p>5 Session I: Equivalence of Complex Products</p> <p>6 FDA Research Update</p> <p>7 Xiaohui Jiang, PhD 24</p> <p>8 Industry Perspective on Generic</p> <p>9 Research Needs</p> <p>10 Robert Bellantone, PhD 35</p> <p>11 Vincent Andolina, BS 45</p> <p>12 Russell Rackley, PhD 50</p> <p>13 Public Comment Period 57</p> <p>14 Panel Discussion 70</p> <p>15 Session II: Equivalence of Locally-Acting</p> <p>16 Products</p> <p>17 FDA Research Update</p> <p>18 Markham Luke, MD, PhD 104</p> <p>19 Public Comment Period 118</p> <p>20 Panel Discussion 130</p> <p>21</p> <p>22</p>	<p style="text-align: right;">Page 15</p> <p style="text-align: center;">P R O C E E D I N G S</p> <p>1 (8:33 a.m.)</p> <p>2</p> <p>3 Opening Remarks – Robert Lionberger</p> <p>4 DR. LIONBERGER: Good morning, everyone. I</p> <p>5 would like to invite the panelists on our first</p> <p>6 panel to come up and please take your seats at the</p> <p>7 panel, and everyone else in the audience to please</p> <p>8 be seated.</p> <p>9 This is the 2017 Generic Drug Research</p> <p>10 Public Workshop. We welcome both all the attendees</p> <p>11 in the conference room and those of you viewing</p> <p>12 through the live webcast. My name is Dr. Robert</p> <p>13 Lionberger, and I'm the Director of the Office of</p> <p>14 Research and Standards in the Office of Generic</p> <p>15 Drugs.</p> <p>16 The purpose of this workshop today is to</p> <p>17 seek input from various stakeholders on research</p> <p>18 priorities for generic drugs. The workshop is</p> <p>19 divided into four sessions. For each session, FDA</p> <p>20 and industry representatives will provide their</p> <p>21 perspective on regulatory science issues for</p> <p>22 generic drug research.</p>
<p style="text-align: right;">Page 14</p> <p style="text-align: center;">C O N T E N T S (continued)</p> <p>1</p> <p>2 AGENDA ITEM PAGE</p> <p>3 Session III: Therapeutic Equivalence</p> <p>4 Evaluations and Standards</p> <p>5 FDA Research Update</p> <p>6 Myong Jin Kim, PharmD 181</p> <p>7 Industry Perspective on Generic</p> <p>8 Research Needs</p> <p>9 Siva Vaithiyalingam, PhD 193</p> <p>10 Public Comment Period 199</p> <p>11 Panel Discussion 216</p> <p>12 Session IV: Computational and Analytical Tools</p> <p>13 FDA Research Update</p> <p>14 Liang Zhao, PhD 257</p> <p>15 Industry Perspective on Generic</p> <p>16 Research Needs</p> <p>17 Amitava Mitra, PhD 271</p> <p>18 Public Comment Period 285</p> <p>19 Panel Discussion 294</p> <p>20 Closing Remarks</p> <p>21 Kathleen Uhl, MD 331</p> <p>22</p>	<p style="text-align: right;">Page 16</p> <p>1 There will also be a public comment period</p> <p>2 in each panel followed by a panel discussion.</p> <p>3 We'll be taking the information that will be</p> <p>4 discussed at this meeting and written submissions</p> <p>5 to the docket in consideration as we develop our</p> <p>6 2018 regulatory science plans for generic drugs.</p> <p>7 So before we begin the meeting, I'd like to</p> <p>8 go over a few logistical items. Please silence any</p> <p>9 mobile devices as they may interfere with other</p> <p>10 people being able to hear the meeting. If you've</p> <p>11 not already done so, please check in at the</p> <p>12 registration desk outside the conference room</p> <p>13 during one of the breaks. Between each session,</p> <p>14 we'll be having a 10-minute break while we reset</p> <p>15 the panelists and speakers and we'll have a one-</p> <p>16 hour lunch break.</p> <p>17 If you'd like to have lunch here during the</p> <p>18 morning break, please go to the kiosk and order</p> <p>19 your lunch during the morning break, and then it</p> <p>20 will be available at lunch, at the lunch break. We</p> <p>21 have overflow rooms behind this room that are set</p> <p>22 up with tables for lunch break, so you'll have</p>

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1 plenty of space here to sit down and have
2 conversations and lunch outside of the hallway.
3 The restrooms are located outside the main
4 entrance, past the registration desk.
5 The workshop is being recorded and
6 transcribed, and there will be both the video
7 recording, and the transcript will be available on
8 the FDA website after the meeting and after they've
9 been prepared.
10 Finally, during each panel discussion, there
11 will be a short public comment period, and we
12 encourage people to not interrupt the session
13 during the public comment period. All the requests
14 to make the public comments were made according to
15 the Federal Register notice, and FDA has notified
16 those who will be speaking during the public
17 comment period.
18 However, during the panel discussion, the
19 moderator or the panelists may ask questions of the
20 speakers from the public comment period, especially
21 if there are any things that they would like to
22 hear more about or follow-up questions. So we ask

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1 that the speakers from the open public hearing
2 remain in the front row so that they are accessible
3 to the panelists for the public discussion. If
4 you're requested by the moderator to speak, please
5 approach one of the two central microphones in the
6 thing.
7 So with those logistical details, I just
8 want to give my introduction here again and remind
9 you of the goals of the workshop. It's to
10 communicate what the current status of regulatory
11 science initiatives for generic drugs are. So in
12 each of the panelists, there will be an FDA
13 introduction that will give our perspective on some
14 of the things we've worked on so far and some of
15 the scientific gaps that are remaining. This
16 should help frame the discussion in the panel.
17 Then we'll be hearing opportunities for
18 industry and the public to provide their input into
19 each panel area, and we've provided opportunities
20 for representatives of the generic industry to
21 participate in each panel, both on the panel and
22 the person making a formal presentation if they

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1 would like.
2 If during the course of the meeting you
3 identify other things that you think we should be
4 aware of and you don't have the opportunity to put
5 them into the record at the meeting, please go to
6 the docket mentioned in the Federal Register notice
7 and submit written comments to that docket. I
8 believe it will be open for approximately 30 days
9 following the meeting.
10 As well, if you go to the Federal Register
11 notice, there is a process for confidential
12 comments. So again, by default, comments to the
13 docket are public, but there is a process outlined
14 by which you can submit comments that may contain
15 confidential information that we would also
16 consider in developing our regulatory science
17 priorities.
18 So if you've participated in this process in
19 the past few years, I think what you'll notice this
20 year is a very different format. So we're piloting
21 this with the panel format of industry and FDA
22 presentations followed by open discussion.

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1 One of the reasons is that we're trying to
2 be responsive to some of the comments from the
3 industry on identifying ways that there could be
4 more back-and-forth engagement and discussion about
5 the regulatory science priorities. We've also
6 tried to, from FDA's perspective, outline some of
7 the things that we think we want to do ahead of
8 this meeting so that we can have feedback and
9 discussion around that.
10 So because this is a new format, you will be
11 receiving a link after the meeting if you signed up
12 to provide some feedback on the format and the
13 balance between presentations and discussion time.
14 So we value that, and we'll use that to optimize
15 the meeting process going forward. So again, it's
16 a new process this year, so we really welcome
17 feedback in terms of making it work better.
18 As we move into the content of the meeting,
19 as we look back over the past five years, what have
20 been some of the impacts of FDA funded research?
21 When I think about these things, I think really of
22 the three large categories of impact: access to

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1 generic products in all product categories;
2 building confidence in generic substitution through
3 strong scientific evidence that supports our both
4 standards for approval and quality of approved
5 products; and developing better tools for the
6 development and review of generic drug
7 applications.
8 This is something that helps both the
9 industry working on developing the products, but
10 also our reviewers evaluating them. So as we
11 advance the underlying science, we can make both
12 the development and review of generic products much
13 more efficient, and that drives a lot of the cost
14 savings that results from generic drugs.
15 For this meeting, we have strongly focused
16 on the first theme here - identifying access to all
17 product categories. And one way to think of the
18 motivation for this is even with the great success
19 of the generic drug program -- so this is directly
20 from the AAM website and their yearly report on
21 generic drugs, most recent one -- 89 percent of
22 prescriptions dispensed in the United States only

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1 account for 27 percent of drug spending.
2 If you do the math on this calculation,
3 you'll see that there's still very large markets
4 without generic competition even though we've
5 reached a high volume of prescriptions. So we want
6 to identify through this workshop what scientific
7 areas can really advance generic competition into
8 all of those markets. We're really focused on
9 that.
10 So today, throughout the four panels, you'll
11 hear 15 proposed research priorities from FDA which
12 we think can accelerate access to generic drugs.
13 And we've really put these out there to really spur
14 the discussion.
15 So we welcome discussion around these
16 topics, input, and alternatives. We'll ask each
17 panel, are there things that we haven't considered
18 that should be on our science agenda. But we
19 really tried to focus the topic for this meeting on
20 what are some of the scientific areas where we can
21 accelerate access to generic drugs through either
22 new bioequivalence methods, where there's no

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1 pathway available, or optimizing existing
2 approaches to make a more efficient approach that
3 works for both product development and product
4 review.
5 So in my slide deck, I have the list of the
6 priorities that we proposed just for the record,
7 but we'll be discussing them in detail in the
8 individual scientific sessions.
9 With that, I'd like to introduce
10 Dr. Stephanie Choi, who is the Acting Associate
11 Director for Science in the Office of Research and
12 Standards. She'll be moderating the first session
13 on equivalence of complex products.
14 I also want to recognize Stephanie. If
15 you've been involved in the logistics of this
16 meeting, you have been directly working with
17 Stephanie. She is really the one that's
18 responsible and deserves all the credit for making
19 this meeting run effectively and well.
20 So I'd like to really recognize her efforts
21 on this, but also introduce her as the moderator of
22 our first session, so welcome Stephanie.

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1 DR. CHOI: Thank you, Rob. The first
2 speaker for our session will be Dr. Jeff Jiang,
3 Deputy Director in the Division of Therapeutic
4 Performance at FDA. And he will be giving an FDA
5 research update on complex drug products.
6 Dr. Jiang, if you can please approach the
7 podium.
8 Presentation – Xiaohui Jiang
9 DR. JIANG: Good morning, everyone. Thank
10 you, Stephanie, for the introduction, and welcome
11 to this public workshop. It is my pleasure, honor
12 to start the first session on equivalence of
13 complex generic products.
14 In the next 15 minutes, I'm going to provide
15 you an overview of our current GDUFA research in
16 this area and show you how we can use
17 characterization and in vitro testing to establish
18 equivalence and help the industry to development of
19 the product as well as for our review to go
20 forward.
21 So first let's have a common understanding
22 of what is a complex product. I'm showing here a

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1 baseline of the published GDUFA II commitment
2 letter, complex product due to either active
3 ingredient, complex active ingredients, complex
4 formulations, complex route of delivery, complex
5 dosage form as well as drug device combinations,
6 although some of them, for example dosage form and
7 formulation, might be overlapping.
8 For this session, as highlighted, we're
9 going to cover most of those categories except the
10 locally-acting drugs, which will be discussed in
11 the next session as well as the drug device
12 combinations.
13 First, let me start on the active
14 ingredients part. This is related to the drug
15 substance. I will discuss our project in this
16 area, then transition into the project related to
17 the product.
18 For this particular area, we have external
19 contracts and the grants ongoing, so those things
20 are focused on a more complex system, namely
21 naturally derived products. We hope our
22 collaborators are using orthogonal characterization

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1 master to elucidate molecular structures as well as
2 their distributions. Furthermore, those
3 characterizations will be tested through some
4 mathematical approach in the research to see how
5 many characterizations are sufficient or needed to
6 establish those equivalents.
7 We also have internal projects running with
8 various laboratories inside the agency. So those
9 projects are more focused on the immediate
10 regulatory needs, for example on peptide-related
11 analysis and the immunogenicity-related evaluations
12 and also some other areas.
13 So the outcome in this particular area, we
14 have been publishing product-specific guidances on
15 specific products, and in the past have been
16 working on glatiramer acetate, sevelamers, then -
17 followed on colesevelam, omega-3 related products,
18 and so on.
19 Another thing on this year's agenda is for
20 the upcoming guidance for highly purified synthetic
21 peptide product, which can reference recombinants
22 with NDA peptides.

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1 In the next few slides, I will highlight
2 some of our internal research outcomes. So in this
3 particular case is the peptide-related analysis.
4 In the past, we have been using the drug substance
5 to do this kind of practice.
6 Shown here is using the drug product of
7 salmon calcitonin. As you can see, on the first --
8 the top chromatograph -- is total iron current.
9 The major peak is the API, but those shoulders,
10 those smaller peaks are peptide-related impurities.
11 The bottom spectrum is ms/ms spectrum,
12 peaking one of the impurity. And really, you can
13 see from that the sequence of that peptide impurity
14 is elucidated at the bottom. By the way, salmon
15 calcitonin is a surrogate to amino acid peptide.
16 So in comparison, the LC-MS-based approach
17 is much more sensitive than the standard USP LC-UV
18 approach as you see in those comparisons. I am not
19 going to into the details. So those are the
20 moving-forward standard with the agency on peptide-
21 related product.
22 The next research project highlighted here

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1 is in the Office of Biotechnology Products by
2 Dr. Verthelyi using the in vitro approach to
3 mitigate or assess some immunogenicity concerns,
4 particularly here, you see, using a cell-based
5 assay to detect inner immune response and modulate
6 impurities. We envision this kind of approach can
7 be used in a comparative study for complex generic
8 products.
9 Now, let me transition into complex
10 formulations at the product level. So here, I'm
11 showing you some examples of what I'm talking
12 about. So I will not go into details for each of
13 those products, but at least you can see how
14 differently those products are.
15 The first thing again is characterization.
16 So we want to use advanced analytics to understand
17 the product attributes as well as those important
18 functional excipients, as well as in addition to
19 develop our analytical method to detect those
20 complex products in the blood, urine, or wherever
21 we can detect them to facilitate the bioequivalence
22 development.

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1 Particularly showing an example here, it's
2 related to the functional excipient in PLGA
3 products. This is our collaborators' work, using
4 C-13 NMR, not only to be able to look in at the
5 details of lactate-co-glycolate, but as well as
6 their ending group.
7 So based on those research outcomes, we
8 updated our product-specific guidance for the
9 products in this area. So not only do we need to
10 look for the Q1/Q2 aspect, we also need to look
11 into the details of those functional excipients.
12 This is another example. This is a study on
13 generic sodium ferric gluconate. We have a
14 research contract ongoing with an outside
15 collaborator as well as an inside collaborator at
16 DARS, looking at the bioanalysis and the clinical
17 BE study designs. But in addition to that, we also
18 performed characterization on the drug product
19 because the iron colloid-related product as well is
20 an important area for us to understand. So shown
21 here is a different orthogonal characterization
22 method we employed to study the particle size

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1 distribution. So that's the continuous. We really
2 try different methods to understand what's going on
3 with this class of drugs.
4 Now let me switch gears to talk about
5 another aspect of product characterization to
6 understand the manufacturing and formulation
7 processes on the end product's quality attributes.
8 Most of those products, as we understand, are sort
9 of required by regulation to be Q1/Q2 to the
10 reference product. However, there's still quite
11 freedom space in that, depending on the
12 manufacturing process impact on the performance of
13 the drug.
14 So this example shown here is a
15 collaboration with the University of Connecticut in
16 Dr. Burgess' lab for risperidone-related products.
17 She developed different formulations using a
18 different approach. As you can see, they
19 themselves are Q1/ Q2 to each other, but however,
20 the characteristics as well as some performance are
21 quite different.
22 So now the final part I'm going to talk

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1 about is in vitro release testing. Traditionally,
2 in vitro release testing has been used as a quality
3 control method, so one of the things is to cover
4 different products.
5 As you can see, ophthalmic
6 suspension/ointments, periodontal, and parenteral,
7 and so on and so forth, as well as different
8 technologies, here some post-release testing
9 methods, USP recommended or FDA recommended, are
10 still quite large and still don't have a
11 recommended method.
12 Furthermore, we want to see if those methods
13 can be further utilized in an in vitro/in vivo
14 correlation manner. And at a certain point with
15 specific products, it maybe can be substituted as a
16 bioequivalence method.
17 So due to the time constraint, in the
18 following slide, I will not go into the details of
19 the research outcome -- the research details -- but
20 I will highlight those projects so that you can see
21 the different areas we are undertaking.
22 This one is ophthalmic drug release.

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1 Ophthalmic drugs are very different, working on the
2 eye. And we want to develop testing that mimics
3 eye viscosity and the flow rate. On the right, we
4 also developed suspension drug products, IVIVC
5 model, in our collaborator's lab.
6 This is showing the microsphere-related
7 product at the University of Michigan. Our
8 collaborator developed a so-called cage model.
9 This model can mimic -- have no impact due to the
10 model itself -- in vitro and in vivo and also will
11 be able to establish some kind of IVIVC.
12 The importance of this model is it gives the
13 developer an opportunity to take those microspheres
14 out so that to study how these things impact on the
15 performance.
16 The last example is related to the progress
17 at the University of Connecticut, working on those
18 formulations. This one is showing really beyond
19 the in vitro release. Also, Dr. Burgess has
20 conducted a study using the in vivo animals, and
21 deconvoluted the profile, and established a very
22 nice IVIVC correlation. So with this process, she

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1 also tested different releasing methods to see how
2 discriminant those things are.
3 So in summary, what I want to point out is
4 advanced analytics is really a cornerstone for the
5 development in this area. For the drug substance,
6 definitely it is necessary to use those techniques
7 to establish the equivalence of active ingredients.
8 Further, for the product, you can capture
9 those critical quality attributes for the
10 equivalence. On the other hand, in vitro testing
11 complements the characterization. It can use a
12 biological test to further confirm identity and the
13 function of the active, as well as measure the
14 performance of the proposed drug product. The
15 in vitro release testing is very promising not only
16 as a quality control method but can step into the
17 bioequivalence paradigm when it is ready.
18 For the panel as well, we hope the
19 discussion will be focusing on four areas. Number
20 one, again, it's on the characterization and using
21 advanced analytics to elucidate chemical
22 composition, molecular structure, as well as the

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1 distribution of active ingredients.
2 The second part is to mitigate certain
3 risks, particularly immunogenicity with a peptide-
4 related product and how we can use in silico, in
5 vitro, and animal studies to reduce such risk.
6 The other two are related to the drug
7 product. One is on the characterization of the
8 product, again, from different angles, looking at
9 particle size, shape, surface characterizations,
10 and many other things to fully characterize the
11 properties of a complex drug product.
12 The last one is how the in vitro BE method
13 can be used. Particularly, we point out the long-
14 acting injectables include suspension as well as
15 microspheres to see which kind of research or
16 advance can help the industry.
17 So without further ado, let me stop here to
18 introduce the next speaker.
19 DR. CHOI: Thank you. Our next speaker is
20 Dr. Robert Bellantone from Physical Pharmaceutica,
21 and he will be giving an industry perspective on
22 generic drug research needs.

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1 Presentation – Robert Bellantone
2 DR. BELLANTONE: Thank you. Good morning.
3 This is kind of strange territory for me. I've
4 never really said anything of note in my whole life
5 in 10 minutes or less except when I say no to my
6 kids when they ask for exorbitant amounts of money,
7 but we'll muddle through and see if we account make
8 it through here.
9 Today we're going to be talking about
10 cyclosporine ophthalmic emulsion, and I'm going to
11 sort of jump to the end. I have a lot of material
12 in the slides. I'm not going to really parallel
13 the slides too much. This is more in the flavor of
14 notes that you might take. So I'm going to talk
15 about what's in the slides, but I'm not going to
16 mimic the order or the detail. This is more
17 supportive detail.
18 So with any ophthalmic emulsion, when you
19 administer, as we know, in the eye, it's got a very
20 short residence time. You blink, half the
21 formulation is instantly gone, and so on, and so
22 forth. So what will happen when you're doing that

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1 is a lot of the formulation goes away. But it is a
2 liquid with a viscosity with a surface tension, and
3 so what will be left behind will be a thin film.
4 That thin film is typically on the order of, say,
5 50 microns in thickness.
6 So this has some profound effects, so I want
7 to talk about that. I also want to talk about what
8 we really can't know about the structure of the
9 globule. So just knowing the particle size will
10 not tell us things about the drug distribution
11 within the globule. And those are the two things
12 that I'm going to focus on, the thin film aspect,
13 and the unknowns in the globule, and how they will
14 carry forward, and how they should be reflected in
15 an in vitro release rate test.
16 We all know that, if you want to do an IVRT
17 for an ophthalmic emulsion or an ophthalmic
18 product, you have a time constraint. There's a
19 short residence time in the eye. But the physical
20 chemistry of the situation also affects and puts
21 time constraints on what you're looking at.
22 This again gets back to the fact that you

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1 have a very thin film that survives the initial
2 blinking. It will get diluted and removed with
3 tears, but you still have processes that go on in
4 the time frame when it's still sitting around.
5 So the two processes that are of main
6 concern in no particular order is, first, because
7 the film is very thin, there's an enormously rapid
8 temperature response. You have a drop, say, of
9 room temperature, 20 degrees C. You administer it
10 to the eye. It comes up -- simple calculation,
11 comes up to the ocular surface temperature or
12 thereabouts in about a second. So you have a rapid
13 temperature distribution.
14 For cyclosporine, that's particularly
15 interesting because cyclosporine, as the
16 temperature goes up, as you would expect, the
17 solubility in the oil goes up, but the solubility
18 in water actually goes down. And this is published
19 data, and we have done determinations and confirmed
20 that.
21 So that is one of the things that goes on,
22 is you have an extremely rapid temperature

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1 response. The other thing that's associated with
2 the thin film is there's not a lot of drug in a
3 thin film. You have an enormous surface area, but
4 you have a very small, shallow drug depot.
5 So what happens is, as the drug is being
6 absorbed or removed, you're going to deplete what
7 it's in the aqueous phase very rapidly. That's
8 typically 5 or 10 percent with the cosolvent
9 effects and so on that we measure.
10 Then what will happen is after you deplete
11 that initial 5 or 10 percent, because of the thin
12 film effect, now you're starting to expose the
13 redistribution of the drug out of the globules into
14 the aqueous phase where they can subsequently be
15 released. And that will actually come in two
16 phases, and I'll show you some data in a minute.
17 Some of the drug gets out of the globules
18 rapidly, and some of the drug that's in the more
19 oil-rich portions of the globule get out of the
20 globule more slowly, and that will limit the
21 release.
22 So those two effects are very important.

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1 The third effect that I want to talk about is with
2 regard to the globule itself. The globules are
3 small, and we like to talk about the distribution
4 in the aqueous phase, the surfactant phase, the oil
5 phase, but there's a problem with that.
6 If you assume no miscibility and you
7 calculate the thickness of the surfactant layer,
8 you would come up with something around 10 or
9 20 nanometers, which coincidentally is around 10 or
10 20 molecules between in thickness. But because of
11 the high miscibility between tween and the oil,
12 that is really not the structure that you have.
13 You have kind of a transition layer.
14 So what I've done in the left-hand panel is
15 I've shown the idealized non-miscible calculation.
16 And I've attempted to show on the right-hand side,
17 for better or for worse, that you have this thin
18 10- or 20-nanometer maybe transition zone, where
19 you have the tween and the oil and water mixed in
20 unknown proportions. And they are going to be
21 process-dependent, we think, because it's not self-
22 emulsifying. So it's not an equilibrium situation.

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1 It may not always go to the same place.
2 Because of that, you don't know the
3 structure inside the globule. You don't know the
4 distribution of the drug inside the globule, what's
5 in the oil-rich versus surfactant phase, and this
6 affects your release. And the takeaway for that of
7 course is just knowing that globule size is not
8 sufficient to predict the release characteristics.
9 One approach that we like to think of is if
10 two formulations are going to behave equivalently,
11 number one, they should start out at the same
12 place. And number two, when introduced into the
13 eye with the rapid temperature change and the
14 depletion of the drug due to release and
15 absorption, they should respond in the same way.
16 Well, in terms of your testing, your
17 parameters to measure, such as globule size and so
18 on, are going to reflect the state of the drug
19 product before you introduce it. The response,
20 which is going to be a function of time, is going
21 to be your release test.
22 So I'm going to skip over this slide. This

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1 is more of an information slide. I said a lot of
2 that already. So let's look at some data that we
3 have generated in our labs. We have technology
4 that was referred to earlier, PMD or pulsatile
5 microdialysis. And this particular technology uses
6 very small geometry set-ups.
7 So the radius of these probes that we use
8 are tubular probes, and we released a drug from
9 them. It's about 100 microns. So you get the
10 rapid temperature jump when exposed to a receiver
11 fluid at a temperature that is different from the
12 storage temperature, and you get rapid release.
13 As we can see from the data here, all of
14 these profiles show basically two phases at early
15 times, say, in the first two minutes -- and we can
16 get that data because of the size of the probes
17 being very small.
18 In the first two minutes, you get a rapid
19 release. Now, we think that the first 5 or
20 10 percent comes from the drug in the aqueous
21 phase. Maybe the next 5, 10, 15 percent is drug
22 that is partitioning out of the globules readily

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1 into the aqueous phase and can be released. And
2 then at later times, 5, 10 minutes on, you get a
3 much slower release. This is reflective of the
4 drug having a slower partitioning out of the more
5 oil-rich phase of the globule into the aqueous
6 phase, and then it can be subsequently released.
7 This is why, when I was looking earlier at
8 the lack of the structure, the clean structure of
9 the surfactant layer, you can't predict that ahead
10 of time. You can only get the effects of all of
11 these things together, the temperature, the depot
12 or lack of, and the redistribution through your
13 release test.
14 So what we did in this slide, the left-hand
15 panel reflects a particular Q1/Q2 formulation, and
16 in that formulation, we released into 20 degrees
17 receiver. It was stored at 20 degrees going in.
18 So there's no temperature effect. This is just the
19 depletion effect, okay, and the redistribution.
20 The higher, the empty squares, the higher
21 plot, is the release into 35-degree medium, and
22 that separates out -- or that's the effect of both

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1 depotting or lack of depotting and the sudden jump in
2 temperature.
3 Now, if you look at the right-hand plots, in
4 the right-hand panel, these are two formulations,
5 both Q1/Q2, but manufactured by different
6 processes, both stored at 20, both releasing to a
7 35-degree medium. And what you see is there are
8 effects of the processing. But with all of these,
9 again, you see the biphasic release.
10 With all of these, because the geometry is
11 similar to what's in the eye and the conditions are
12 similar to what the thin film is exposed to in the
13 eye, we're able to get this data at early times,
14 and that is critical. And that has very little to
15 do with the residence time and a lot to do with the
16 physical chemistry and fluid dynamics of what's
17 going on with the formulation.
18 So we think that's a really good test. And
19 we think that any test should reflect the ability
20 to redistribute, the ability to mimic the
21 temperature changes, and so on. If you don't have
22 those, we don't think it's a good test because

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1 you're not looking at the right circumstances that
2 govern whether two formulations are equivalent in
3 their behavior in vivo.
4 I just want to make a comment because I've
5 been on record as being critical of using Franz
6 cell tests for this. And the Franz cell gives you
7 none of those, so I'm going to move on to the last
8 slide. But you can read about how Franz cells do
9 not allow you to do that.
10 So in summary, those are the takeaways. We
11 feel that we've described an appropriate test, and
12 with that, I'll say thank you very much to the FDA.
13 And also, I would like to thank you all for
14 listening. And thanks to Piyush Patel and Kosha
15 Shah, two scientists who have helped me drive the
16 bus on this project.
17 Thank you.
18 (Applause.)
19 DR. CHOI: The next speaker is Mr. Vincent
20 Andolina from AuroMedics Pharma, and he will be
21 giving us the second industry perspective on
22 generic drug research needs.

<p style="text-align: right;">Page 45</p> <p>1 Presentation – Vincent Andolina 2 DR. ANDOLINA: Good morning, and thanks, 3 everyone. I won't focus on the science, but more 4 the regulatory since this was the only iron colloid 5 product with an AB rating. So my interest is how 6 that happened and how there have been none since. 7 Next is my disclaimer. These are only my 8 opinions, and I'm not trying to disclose any 9 confidential or trade secret information. 10 As Dr. Jiang spoke, establishing sameness, 11 it's difficult if the RLD is not completely 12 characterized as heterogenous or otherwise 13 variable. And if it's patented, how do you show 14 sameness without infringing? There is some 15 differences permitted, for example impurities 16 profile. However, if the impurities are suspected 17 of immunogenicity, that causes further study. 18 Representative iron colloid products are 19 polymers of variable molecular weight: iron dextran 20 the first; sodium ferric gluconate in sucrose; iron 21 sucrose, which is Venofer; ferumoxytol; and ferric 22 carboxymaltose.</p>	<p style="text-align: right;">Page 47</p> <p>1 thermodynamic equilibrium, we thought it would be 2 eligible for a biowaiver. 3 We proceeded to have the product developed. 4 No bioequivalent study was conducted. We 5 manufactured an exhibit batch according to the 6 requirements of the time and got our Refuse-to- 7 Receive. Again, I want to point out the path 8 forward was discussed via teleconference, which 9 would not happen today. 10 Our first substantive review by a chemist 11 resulted in a major deficiency. The chemist is 12 part of today's panel. Again, the path forward was 13 explained to us by the chemistry team leader and 14 the review chemist by phone informally, which was 15 immensely helpful in actually getting the product 16 approved and in agreeing on a path forward. 17 Our request for a waiver of bioequivalence 18 was ultimately rejected, and we were asked to do a 19 bioequivalence study along the lines of a 20 bioavailability study that was done on behalf of 21 the reference product using a compartmental model. 22 Let me just say a couple of words about</p>
<p style="text-align: right;">Page 46</p> <p>1 Iron dextran was the first, and the labeling 2 contains a boxed warning of the risk of 3 anaphylaxis. There are two products marketed and 4 approved that differ in molecular weight and are BP 5 rated, not substitutable. 6 The next is the compound of interest for 7 this presentation, sodium ferric gluconate complex 8 in sucrose. The RLD is Ferlecit. The generic was 9 approved based on bioequivalence and extensive 10 physicochemical characterization studies. 11 Iron sucrose is probably the market leader, 12 or it was back then. It is Venofer. Ferumoxytol 13 is a newer variant. Ferric carboxymaltose is from 14 Luitpold, who markets Venofer. 15 Now, the actual submission. Sodium ferric 16 gluconate was developed by a virtual company, 17 GeneraMedix. All lab work was performed by 18 contractors or partners. The initial information 19 transfer from FDA was done by telephone, which 20 would not happen today. We were told that, if it 21 was Q1/Q2, physicochemical characterization, and if 22 the drug product could be shown to be a solution, a</p>	<p style="text-align: right;">Page 48</p> <p>1 that. Iron is conserved by the body. Injectable 2 iron, colloids, you cannot inject ferric chloride. 3 It's toxic. That could not be injected. And 4 furthermore, labile iron or free iron is considered 5 to be the impurity of -- you might call it -- of 6 most interest for toxicity. 7 The original bioavailability study that was 8 published used a compartmental model. Injected 9 iron is taken up by the reticuloendothelial system 10 and then sent back into the body in the form of 11 transferrin- bound iron, which is obviously not 12 toxic. 13 We had a bioequivalence study performed with 14 a relatively small sample size and a crossover 15 design. Ultimately, that bioequivalence study was 16 rejected, again with extensive communications with 17 the Division of Bioequivalence. 18 We went forward with a parallel 19 bioequivalence study using conventional data 20 analysis. That was also informally reviewed by the 21 Division of Bioequivalence, again something that 22 would not happen today, I can assure you. The</p>

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1 second study was conducted, submitted, and accepted
2 in 2009. Actually, just to see how fast the time
3 was, dosing was in June. We submitted the study in
4 September. We got an acceptance by the
5 bioequivalence division in November.
6 As of September 2010, the ANDA was
7 approvable as far as OGD was concerned. It was
8 waiting for a citizen petition to be responded to.
9 That was done on March 31, 2011, at which time the
10 ANDA was approved. There is a draft guidance on
11 SFG, as we call it, published. It gives the
12 bioequivalence parameters and the physicochemical
13 characterization parameters.
14 I would say the paradigm of FDA doing
15 research and telling industry what they should do
16 at an arm's length is difficult because industry
17 doesn't know what they need to do, what results
18 will be approvable, and so on.
19 To get more feedback is difficult today.
20 You can submit a control correspondence. That has
21 limitations. Any other kind of feedback, you can
22 ask for a meeting. That also doesn't work that

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1 well now. In my recent experience requesting a
2 meeting, it takes about a month to see if the
3 meeting will be granted, and it must be scheduled
4 or you're told that it'll be done by e-mail.
5 Again, if it's by e-mail or on paper, there's no
6 back and forth. There's no opportunity to reach a
7 consensus on the path forward.
8 So that's my little soapbox speech for the
9 day, and thanks, everyone.
10 (Applause.)
11 DR. CHOI: The last speaker for the session
12 is Dr. Russ Rackley from Mylan Pharmaceuticals, and
13 he will be giving us the third industry perspective
14 on generic drug research needs.
15 Presentation – Russell Rackley
16 DR. RACKLEY: Thank you for the opportunity
17 to present this afternoon. Again, I want to speak
18 to the challenges of demonstrating statistical non-
19 inferiority for irritation transdermal drug
20 delivery systems using the OGD guidance. Just to
21 comment, this reflects my views, not the official
22 opinion or policy of Mylan.

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1 So the problem previously with adhesion and
2 still currently with irritation is that using the
3 OGD's method for good-performing products,
4 irritation scores approach zero. And thus, the
5 non-inferiority margin is proportional to the mean
6 score for the reference.
7 The consequence of that is the non-
8 inferiority margin essentially approaches zero.
9 This makes this requirement practically one of
10 demonstrating superiority to a good product and may
11 require extraordinary powering requirements.
12 So thus, it's believed that the current
13 guidance, although not intended to do so,
14 effectively serves as an inappropriate block to
15 generic approvals.
16 Let's take a look at the statistical metric.
17 It's based on the upper 95 percent confidence
18 interval of the mean test score minus 1.25 times
19 the mean reference, which must be shown to be less
20 than zero. This equation can be rearranged to
21 demonstrate the reference mean score is a
22 denominator. And as you know, as denominators

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1 approach zero, this could be problematic for
2 inflating the metric and meeting this criteria.
3 I tried to illustrate this a little more
4 graphically here. The line of identity here is the
5 blue line, which reflects equivalent scores for
6 test and reference products. The evenly dashed
7 line here is the current irritation guidance margin
8 for non-inferiority. And I've shown the uneven
9 dashed line as for comparison for the adhesion, a
10 non-inferiority margin.
11 I will comment that I think with the new
12 adhesion guidance, this is an improvement that
13 solves a problem partially, but still seems to be
14 somewhat rigid. So this orange area seems to be an
15 area qualitatively you can say forces a test
16 product to perform in a somewhat more superior
17 manner than necessarily demonstrating non-
18 inferiority.
19 So again, on the adhesion metric, this just
20 compares the old metric and the current irritation
21 metric to the current adhesion metric, which is the
22 mean of the test minus the mean of the reference as

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1 the upper 95 percent confidence interval, which is
2 less than or equal to 0.125.
3 Again, I think this seems to be still a
4 fairly rigid criteria, still working and
5 understanding how well that works. Perhaps it
6 could be overly conservative, but I'd request maybe
7 that we better understand the rationale for the
8 0.15 criteria.
9 I thought I would give a couple of examples
10 here to show how the current irritation metric
11 works. This is a study with 36 subjects who were
12 evaluated in a 21-day same-site irritation
13 application of a transdermal drug system patch. It
14 was applied daily for 21 days. And you'll see that
15 the trends here are that the scores on a potential
16 scale of 0 to 10 are around 1 to 2 and maybe
17 tailing off past that for both test and reference.
18 To better illustrate that with this
19 histogram, you see fairly similar behavior of the
20 cumulative irritation over 21 days. So these seem
21 to be fairly comparable in performance.
22 When the metric is applied in this case,

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1 you'll see that the mean test and reference test
2 scores are around 2, so the parameter test
3 minus 1.25 reference gives an upper 95 percent
4 confidence interval less than zero. So in
5 conclusion, this particular case, the product
6 passed with this kind of cumulative irritation.
7 In a second example, we had a 78-subject
8 study evaluated 21 days of a cumulative irritation,
9 again transdermal drug delivery system, comparisons
10 that were twice-weekly patches. So there are 6
11 applications over the 21 days. And you'll see the
12 trends here that the scores largely remain around
13 zero.
14 Illustrated as a histogram, again, you see
15 fairly comparable performance from both test and
16 reference for these products, which largely are
17 centered on zero, indicating no irritation. The
18 current metric applied to this data, you'll see the
19 means are very close to zero, 0.113 for the test,
20 0.088 for reference. So the end result of this
21 upper 95 percent confidence interval for the
22 current metric is slightly above zero, so the

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1 product would fail on that case.
2 So the current guidance suffers from the use
3 of non-linear discrete scale, particularly for
4 irritation results and datasets consisting largely
5 of zeros. As a result, as the reference mean score
6 approaches zero, the non-inferiority margin
7 essentially disappears, which has the effect of
8 forcing a generic to perform in a superior manner
9 or could require powering with an extraordinary
10 high numbers of subjects.
11 So we feel there's a need for an updated
12 non-inferiority testing method and understanding
13 the current method for adhesion in the modification
14 on the irritation method, so that we can span the
15 spectrum of reference performance, particularly for
16 well-performance reference products, that
17 predominantly score as zeros on both cases.
18 I'd just reflect just one situation. This
19 has been well-known I think for some time. There
20 was a submission by Teva for a testosterone gel. I
21 think it was originally submitted as a generic
22 product, so the test aligned with that kind of a

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1 program. However, they ran into this similar
2 problem, apparently with respect to scoring zeros,
3 according to the irritation scale, and suggested
4 this "+1" approach to solve this particular issue.
5 The filing was eventually converted to a
6 505(b)(2), and it was eventually approved on the
7 basis of showing neither cumulative irritation or
8 sensitization reaction occurring to study subjects.
9 But the "+1" method proposed basically takes the
10 OGD method and adds 1 to all possible scores.
11 If we took this scale modified and applied
12 it to the second zero that I showed you that
13 failed, you'd have means that come out right around
14 1 because that's the lowest score you can get. And
15 the metric then shows the 95 percent confidence
16 interval slightly below zero. In this case, it
17 would pass.
18 So the issue continues as a regulatory
19 science issue, and we urge the FDA to address it in
20 the coming year as a priority since the effect of
21 inhibiting generic competition for well-performing
22 products is counter-intuitive to public health

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1 considerations, we feel.
2 So there are some questions to ponder, and I
3 know the agency is currently working on the
4 irritation guidance but acknowledge that the
5 current metrics for non-inferiority testing need to
6 be modified to accommodate all types of product
7 responses.
8 Can OGD promptly provide an alternative
9 method for generic companies to fairly compare
10 their products to RLDs across a full range of RLD
11 responses anticipated for both adherence and
12 irritation; and to that end, seek some rationale
13 for the current adherence criteria?
14 That's all I have. Thank you.
15 (Applause.)
16 Public Comment Period
17 DR. CHOI: I'd like to thank all the
18 speakers for this session. We will now hold the
19 public comment period for this session. And the
20 first speaker is Dr. Jon de Vlieger from the
21 Nonbiological Complex Drugs Working Group.
22 DR. de VLIEGER: Thank you very much for

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1 your introduction.
2 Good morning. My brief comments today, I
3 intend to address the topic of nonbiological
4 complex drugs, which I will refer to as NBCDs in
5 the remainder of the talk.
6 Before starting, I'd like to say that I'm an
7 employee of Lygature. It's a Netherlands-based
8 independent, not-for-profit organization formerly
9 known as Top Institute Pharma, and we coordinate
10 public-private partnerships in the area of
11 pharmacotherapy and medical technology. And as
12 part of our regulatory innovation portfolio, we
13 host the NBCD working group as the start of the
14 discussions on this topic from 2009.
15 So when looking at the complex drugs
16 products landscape and the challenges involved in
17 developing generics similar or follow-ons of these
18 types of products, you may plot the different
19 product families in this landscape slide, where on
20 the lower side, you would see the challenges in
21 demonstrating bioequivalence of these product
22 families, and on the Y-axis, you will see the

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1 challenges in demonstrating pharmaceutical
2 equivalence.
3 The NBCDs are a subgroup of complex drug
4 products, indicated in blue. You will notice a
5 green thin line around some of these products,
6 which are in other parts of the world referred to
7 as biologics, but in the U.S. regulated as drugs.
8 It's apparent that this landscape here is just an
9 illustration, and in the future, there many more
10 product families to be plotted in here.
11 To fully understand the challenges involved
12 in the development of these type of complex
13 products and its generics, similars, or follow-ons,
14 the NBCD working group truly believes that multi-
15 stakeholder scientific discussions assist in
16 showing the advances we've made as a community
17 together and also outlining the challenges faced
18 that we still need to solve.
19 This is an example of a report published
20 earlier this week on one of those multi-stakeholder
21 scientific discussions at the New York Academy of
22 Sciences. In this white paper, the authors from

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1 different types of stakeholders in the discussion
2 have listed outstanding challenges that as a
3 scientific community we need to solve, and I've
4 highlighted them here.
5 First of all, the assessment of critical
6 quality attributes to establish the equivalence of
7 these generics, follow-on, or similar products
8 questions, in addition, are who is going to define
9 them, who is responsible for defining them, and how
10 are we going to do that as a scientific community?
11 The other point is the need to publish
12 scientific findings in the public domain to further
13 the progress in the field. I'm very pleased to see
14 that the last two years, actually, all stakeholders
15 really stepped up their game, including the FDA, of
16 publishing their scientific findings in this area.
17 So let's all continue doing this. It helps the
18 discussion based on the data that is available in
19 the public domain.
20 The necessity to develop worldwide consensus
21 and regarding nomenclature and labeling of complex
22 products and regulatory actions when substandard

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1 complex products are identified, the group is
2 committed to further these discussions in other
3 meetings next week in Basel during the CLINAM
4 conference and the Pharmaceutical Sciences world
5 conference in Stockholm.
6 So I encourage all stakeholders to
7 participate in these discussions so we can make
8 sure that products developed are of high quality
9 and high safety. Thank you very much.
10 (Applause.)
11 DR. CHOI: The second speaker is Dr. Amy
12 Barton Pai from the University of Michigan.
13 DR. PAI: Good morning. What I'd like to do
14 today is essentially discuss how we can leverage
15 global experience with iron sucrose generics to
16 potentially augment bioequivalence evaluation in
17 the U.S.
18 Iron sucrose is a smaller molecular weight
19 compound. It's widely used, and it is the most
20 commonly used product in dialysis patients. More
21 than 30 percent of U.S. dialysis patients receive
22 almost 5 grams of elemental iron annually. This is

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1 in comparison to the average healthy person that
2 absorbs about 1 to 2 milligrams. So while the
3 dosing of iron and amount we give is controversial
4 and beyond the scope of this presentation, I think
5 what it does is underscore that we need safe
6 products.
7 Many iron sucrose similars are available in
8 Europe, Asia, and South America, and switches are
9 often mandated. The emerging published data on
10 these products across the translational research
11 continuum has been emerging and I think gives us an
12 interesting framework that really does implicate
13 labile iron as being associated with adverse
14 effects.
15 Animal data has clearly shown that these
16 iron sucrose similars are referred to as such
17 because, ultimately, the challenges we're
18 discussing today and the challenge in creating an
19 exact copy has been shown to increase oxidative
20 stress.
21 Across a more translational spectrum from
22 cell to animal to human, again we have shown

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1 repeatedly that iron sucrose similars in comparison
2 to control or RLD increase oxidative stress and
3 potentially vascular damage.
4 Then ultimately, we are seeing clinical
5 outcomes data, which are showing increased adverse
6 effects that are typically associated with labile
7 iron such as hypotension, reactions with infusion,
8 and lot-to-lot variations.
9 These are data from a U01 that was recently
10 funded. Essentially, we strived to identify the
11 optimal labile iron assay, which was an HPLC-based
12 assay with a deferoxamine chelation method.
13 Here what we show is the in vitro labile
14 iron release profile in saline and in serum, and
15 then also in vitro in a rat model. Ultimately,
16 when we're looking at this only-approved U.S.
17 generic, which is sodium ferric gluconate complex,
18 what we've shown is there is no statistically
19 significant difference in labile iron, although we
20 can see some observation that Ferrlecit, for
21 example, has more variability in vivo and is higher
22 in vitro.

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1 So just to tee this up, we believe that
2 labile iron release profiling is a pragmatic
3 approach to augment physicochemical
4 characterization. We believe there are inherent
5 PCC challenges that are widely observed in this
6 group certainly. We think labile iron profiles are
7 informative to confirm that no significant
8 difference exists in the rate and extent of labile
9 iron, and it supports other in vitro dissolution
10 techniques.
11 So ultimately, we believe bioequivalence as
12 expressed here is uniquely challenging, and we
13 believe labile iron profiling would be a
14 significant addition to bioequivalence evaluation.
15 Thank you.
16 (Applause.)
17 DR. CHOI: The next speaker is Dr. Kenneth
18 Morris from Long Island University and also
19 representing NIPTE.
20 DR. MORRIS: Thanks, everybody. As said,
21 I'm from Long Island University. And for those of
22 you who don't know, I'm from the Brooklyn campus,

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1 so traffic here is no surprise.
2 So today, what I'd like to really briefly
3 discuss in the context of NIPTE is the advanced
4 analytical techniques that can be used to address
5 many of the problems that we find occurring both in
6 the branded and generic industry.
7 NIPTE, as you may or may not know, is 17
8 universities. As far as we know, it's the largest
9 collection of pharmaceutical, industrial pharmacy
10 programs in the country and probably the world,
11 which makes it unique in that sense of course. And
12 it has both a science and an education mandate and
13 mission, and we'll talk more about that this
14 afternoon and in the later session.
15 So today I'm actually presenting some work
16 that was a culmination or a summary of some work at
17 three different NIPTE schools, Minnesota, Kentucky,
18 and a little bit from a couple of other schools,
19 really.
20 The first example that you can
21 see -- there's one behind me, too, in case you
22 didn't know -- is looking at salt

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1 disproportionation in situ in a tablet. This is
2 using synchrotron radiation. So the idea here is
3 to be able to map the tablets' occurrence of the
4 freebase and the salt that forms.
5 This is pioglitazone. And as you can see in
6 the upper-right figure there, the tablet is mounted
7 in a special holder, and then at increments of
8 300 microns, spectra, powder patterns are
9 collected. And what you see is that using the
10 transmission mode of the x-ray, we can map the
11 conversion as I said.
12 I forgot my next point, but fortunately for
13 three minutes, I've made notes. So good evening,
14 we've already done that. So the extent of
15 transformation at the edge was found to be about
16 five times what it was in the core, which was what
17 you expect, but this is actually a quantitation of
18 that as opposed to just relying on the physical
19 chemistry that we know must be the case.
20 Also, if you look at the longer term, that's
21 over a 2-hour period, over 9 days, we can see that
22 that pattern persists, so that even over relatively

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1 realistic times for exposure, you can assess these
2 problems.
3 This is the sort of thing that's very
4 difficult to quantify. And the impact on
5 dissolution, we'll deal with in the next slide a
6 little bit with a different example. But the point
7 is that material science for pharmaceuticals --
8 (Timer sounds.)
9 DR. MORRIS: You don't have to go home, but
10 you can't stay here. Sorry. I'll pick up a little
11 of this, this afternoon. Thank you.
12 DR. CHOI: The last presenter is Dr. Duxin
13 Sun from the University of Michigan.
14 DR. SUN: Thank you very much. In the past
15 five years, we extensively studied the clinically
16 available non-particle formulation, mainly the
17 injectable complex formulation for their
18 distribution and pharmacokinetics.
19 We observed some of the challenges in terms
20 of BE studies. Number one, the plasma AUC to Cmax
21 may not be able to distinguish the difference
22 between brand and generic.

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1 Two, the total drug concentration in plasma
2 may not tell whether the drug and carrier go
3 together or disassociate.
4 Number three, the formulation may have
5 different intracellular uptake, although they have
6 the same plasma concentration.
7 Number four, even though they have a similar
8 plasma concentration, we have a tissue-specific
9 distribution; therefore, that's linked to unique
10 toxicity, unique efficacy.
11 I show you this data for each of these
12 statements. We did a lot of clinical available
13 nanoparticles, but I only have time to show you
14 two. One is the paclitaxel micelle formulation.
15 One is abraxane, which is the albumin-based
16 formulation.
17 We know they are not BE because they have a
18 different indication, different toxicity profile,
19 and a different usage. However, if you test it in
20 a human, the left panel, the very left panel -- if
21 you test it in a human, paclitaxel and abraxane,
22 their AUC if you adjust them are almost identical.

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1 Based on this standard, they are considered
2 BE, however, we know they are not. But then, how
3 do you distinguish those two based on this plasma
4 profile? There's a subtle difference. We have not
5 figured out the subtle difference, how to tell a
6 difference yet.

7 Number two, left panel, in human, you cannot
8 tell whether the drug carrier complex go together
9 or separate. The brand name claims they go
10 together, but you just cannot tell. But in the
11 right panel from the mouse, you could tell because
12 they do go together in mouse. If they do not, you
13 will see a similar plasma profile between
14 paclitaxel and abraxane. So the two different
15 species can tell the difference. Can we use that
16 somehow for the BE standard in the future?

17 Number three, although you have similar
18 plasma profile between paclitaxel and abraxane, and
19 also if you make a poor quality of albumin
20 formulation, they are similar in plasma profile.
21 However, if you see the intracellular drug uptake,
22 clearly, abraxane is much, much higher than

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1 paclitaxel and a poor formulation of albumin. So
2 how do you distinguish that from plasma profile?

3 Number four, even though they have a similar
4 plasma profile, however, they have very different
5 tissue distribution in fatpad, in pancreas, in
6 lung, in others. The formulation also shows the
7 difference. Based on those observations, we think
8 we should make a different formulation. We should
9 steady their distribution by imaging. And also, we
10 should do a somewhat PBPK to really optimize the
11 current BE standard. Thank you.

12 (Applause.)

13 Panel Discussion

14 DR. CHOI: I would like to thank all the
15 speakers who provided comments during this public
16 comment period. We will now hold the panel
17 discussion to discuss research priority areas for
18 complex generic drug products. And before we
19 begin, I would like to ask each of the panel
20 members to state their name and affiliation,
21 beginning with Dr. Jeff Jiang.

22 DR. JIANG: Yes. This is Jeff Jiang. I'm a

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1 Deputy Director of Therapeutic Performance under
2 Office of Research Standards and OGD.

3 DR. BURGESS: Diane Burgess, University of
4 Connecticut School of Pharmacy.

5 DR. CONNER: Dale Conner. I'm Director of
6 the Office of Bioequivalence in the Office of
7 Generic Drugs in CDER.

8 DR. KEIRE: David Keire. I'm the Director
9 of the Division of Pharmaceutical Analysis within
10 the Office of Testing and Research at OPQ.

11 DR. KOZAK: David Kozak in the Division of
12 Therapeutic Performance. I'm a team lead
13 underneath the Office of Research and Standards.

14 DR. RAW: I'm Andre Raw. I'm the acting
15 scientific and policy advisor at the Office of
16 Pharmaceutical Quality, Office of Life Cycle Drug
17 Products.

18 DR. ROSENBERG: Amy Rosenberg. I'm a
19 Division Director in the Office of Biotechnology
20 Products in CDER and the supervisory medical
21 officer.

22 DR. SRINIVASAN: Aloka Srinivasan, vice

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1 president, Lupin Pharmaceuticals.

2 DR. STRAUSS: David Strauss, Director of the
3 Division of Applied Regulatory Science in the
4 Office of Clinical Pharmacology and Translational
5 Sciences in CDER.

6 DR. TYNER: Katherine Tyner, Acting
7 Associate Director of Science in the Office of
8 Pharmaceutical Quality, CDER.

9 DR. VAITHIYALINGAM: Siva Vaithiyalingam,
10 regulatory affairs, vice president, Lupin
11 Pharmaceuticals.

12 DR. VELAGAPUDI: Raja Velagapudi, the
13 executive director of clinical development, Sandoz,
14 Inc.

15 DR. CHOI: Thank you. As was presented by
16 Dr. Lionberger during the opening remarks, FDA
17 proposes 15 research priorities to help accelerate
18 access to generic drugs. We would now like to
19 obtain input from our panel on the priorities that
20 relate to complex drug products. The first
21 proposed priority area is for new advanced
22 analytics for characterization of complex active

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1 ingredients.

2 Elucidating the chemical composition,
3 molecular structure, and distribution of complex
4 APIs can present a number of characterization
5 challenges. And I'd like to ask Dr. Andre Raw to
6 start off this panel discussion by commenting on
7 the current scientific gaps and regulatory
8 challenges for establishing active ingredient
9 sameness for complex APIs.

10 DR. RAW: In the recent history, we have
11 approved complex APIs that are highly heterogenous
12 active ingredients. And if you really think about
13 it, the way that we distilled it was based upon
14 considerations of obviously the molecular
15 structures and their physicochemical
16 characteristics, but other properties, including
17 the sourcing of the material, whether it's
18 synthetically sourced, or whether it's completely
19 synthetically derived, or whether it's a
20 combination of the two, naturally sourced or
21 synthetically derived such as Lovenox, such as low
22 molecular-weight heparin.

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1 Based upon these three attributes, we
2 actually were able to develop criteria that
3 informed the approval of enoxaparin, iron colloids,
4 glatiramer acetate, and the current guidance says
5 we have for Premarin as well as sevelamer.

6 So these are definite doable problems. We
7 account definitely address these issues. However,
8 I think the challenges that we have is that each
9 API is unique, and for each API, we have to develop
10 tailored criteria -- equivalence criteria -- to
11 address based upon the structures, its sourcing,
12 and biological chemical characteristics to address
13 this. And this does present challenges for
14 scientific as well as regulatory that both FDA and
15 industry have to -- it's sort of a learning curve
16 to address these things. But that's my comment.

17 DR. SRINIVASAN: Incredibly interesting
18 presentation. And Vincent, thank you for bringing
19 back memories about the iron -- and I do think that
20 FDA has made incredible strides in the area of
21 complex generics, but every complex generic is
22 complex in its own way. Like Tolstoy said, every

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1 unhappy family is unhappy in its own way. Every
2 happy family is the same.

3 So it's the same way here. What I think
4 industry is looking at is we do not want a changing
5 target. The problem with the generic industry is
6 it has to move very fast. I mean, there are 15
7 companies who are doing it. I think it's good to
8 come out and talk about it. It's highly
9 competitive. It's also working on a shoestring
10 budget.

11 So what we are expecting from FDA on this is
12 also guidance and, in some cases, probably the
13 minimum criteria, because there is a destination,
14 and you can reach it in a red 2017 Ferrari or a
15 2010 Honda Civic. Now, the question is -- both are
16 going to take you there -- I mean, I know it's cool
17 to reach that in the Ferrari, but can I use the
18 Honda Civic?

19 I'm sorry for that. I couldn't think of
20 anything else. But the question is to come to a
21 point and understand what is enough. And there may
22 be points where it's not enough. And at that

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1 point, go and say, you know what? We are not
2 comfortable. I think we need a clinical endpoint
3 study here.

4 That's also acceptable. What the industry
5 is looking for is some kind of consistency.

6 Recently, there are rare experiences with products
7 like teriparatide and liraglutide, et cetera, which
8 are rDNA origin.

9 We all know. I mean, some of us from FDA
10 OGD knew that probably it would be tough to go
11 without rDNA, but there wasn't a very clear
12 directive there, which put people into a little bit
13 of problem. And we would hope -- I mean, these are
14 great, and we want to work with FDA on this, but we
15 would want them to be consistent in their advice.

16 DR. ROSENBERG: This is clearly a critical
17 priority. And I think one thing that is of great
18 importance is, when you identify perhaps new
19 species, new molecular structures, how are you
20 going to determine what is a critical attribute and
21 what is a non-critical attribute? Because that to
22 me is the next absolutely most important step

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1 because that will determine essentially what you
2 have to focus on. And if you can't decide if it's
3 a critical attribute or not, then you're uncertain,
4 and how should you manage that kind of uncertainty?
5 We've published papers on managing
6 uncertainty regarding this kind of issue, but I
7 would turn it back to Andre and say, you identify
8 new attributes. How are you going to determine if
9 they're critical?
10 DR. RAW: Yes. So one thing that is alluded
11 to is we have new attributes, like for example an
12 impurity. Okay? And the question is, can we
13 develop -- how do I say?
14 One of the things that is a challenge is
15 immunogenicity, for example. And how can we
16 address models, that are potentially in vitro
17 models or animal models, that potentially could
18 address these to resolve these uncertainties that
19 we have?
20 DR. KEIRE: Yes. I think some of the models
21 that Daniela Verthelyi in your group is working on
22 are examples of that, the cell-based models, innate

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1 immunity that can be used to screen these things,
2 once you identify them with the advanced analytics.
3 Right?
4 I think the paradigm has shifted where
5 before you didn't know they were there. And even
6 if you could know they were there, you didn't know
7 what they were. Right? You just had these little
8 peaks. You could maybe get a mask if you couldn't
9 identify them.
10 But now the technology has changed. It's a
11 good time to be an analytical chemist, maybe not a
12 good time to be a regulator because all these new
13 things are coming. So one approach could be you
14 could look about what's safe and effective in the
15 marketplace right now. What's in those products
16 that we didn't know was in there before. And at
17 least that's a starting point for some risk
18 assessment. So I think that's the process we're
19 thinking about.
20 DR. ROSENBERG: Yes. I don't think we
21 should focus strictly on immunogenicity, although
22 that's very important. But there may be other

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1 attributes that impact other aspects of behavior.
2 DR. CHOI: Dr. Burgess?
3 DR. BURGESS: Yes. I just wanted to mention
4 an example from recent work in my lab with OGD,
5 where we've been looking at polymers, particularly
6 PLGA. And we found that very subtle differences in
7 the polymer that you wouldn't have expected have
8 had significant effects on drug release in vitro at
9 least, and we're now studying that in vivo. And
10 this could impact a burst-release in vivo that
11 could affect the efficacy as well as the toxicity.
12 These kind of changes I'm looking at are
13 with polymers that are purportedly equivalent in
14 molecular weight, in copolymer ratio and n group,
15 but still subtle differences that may be associated
16 with different manufacturing from different sources
17 of manufacturers and could result in, for example,
18 different blockiness or something like that within
19 the copolymers.
20 Those subtle differences may impact on some
21 types of products and may not impact in other
22 products. And this is something that we think is

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1 important to investigate because of the potential
2 for safety and efficacy.
3 DR. SRINIVASAN: That's so interesting, and
4 that probably brings to another topic about the
5 timing because industry has started working on this
6 probably in 2013-14, if not before, on these
7 complex injectables, to bring them to FDA.
8 I think there seems to be a lag, but FDA has
9 started the work now. Most of them are quite
10 advanced in their research, and it would have been
11 so helpful to have a little earlier advice from FDA
12 on that. And that's also for the future generics,
13 something to be considered, that work usually
14 starts five years before for these products.
15 DR. CONNER: I just want to readdress what
16 has been talked about, that generic drugs in the
17 U.S., in our system, depend upon an inherent
18 assumption that the drug substance is the same when
19 you compare them.
20 So we take for granted these days that
21 simple small molecules are very easy to
22 characterize. We don't have any worries that

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1 they're the same thing. Impurity profile is a
2 different story, but at least we know that the drug
3 substance is the same.
4 If you went back 30 or 35 years, that wasn't
5 true. Even simple molecules were sometimes very
6 hard to characterize analytically. And
7 advancements in science bring us to a point today
8 where we almost take that for granted. Simple
9 molecules can be fully characterized. We know what
10 they are, and we know when they're the same and we
11 know when they're not.
12 So I think that the advances for more
13 complex situations, the advances in analytical
14 chemistry is critical. And someday, I'm sure we'll
15 be sitting in a meeting like this, all taking for
16 granted that even these very complex molecules can
17 be fully characterized. But that will be based on
18 the advancement of technology, of which meetings
19 like this, the FDA research program, and industry
20 and academic research programs, will all lead to
21 that.
22 I also hear two levels -- I've heard two

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1 levels of complaining in a certain area, one that
2 things move too slowly. I've been here for a while
3 and people were saying, this is a complicated
4 product, and the FDA's not giving us guidance. The
5 science just wasn't there. I mean, in a lot of
6 cases, we don't know.
7 As science advances -- and it's almost
8 snowballing now due to all these programs -- we get
9 advancements in the areas we need more and more
10 quickly. So when you perceive changes in guidances
11 and changes in thinking both on the industry side
12 and the FDA side, that's due to we have now new
13 information and better, or worse from some points
14 of view -- we're getting it faster and faster.
15 The FDA is now very good at taking
16 information, kind of mulling it over very quickly,
17 and bringing it out to the public in a guidance,
18 and we're getting better and better and faster and
19 faster at that. So some see that as a
20 disadvantage, but I really see it as an advantage.
21 I mean, if you're in business, and you're on
22 a clock, and you're on a schedule, that may come at

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1 a very inopportune time for you. But it's the
2 advancement of science. It's the advancement of
3 regulatory knowledge. And with all these research
4 efforts, it's going to get faster and faster, we
5 hope. And someday, we'll all be taking this for
6 granted.
7 DR. CHOI: Thank you. I'd like to move to
8 the next proposed priority area. For generic
9 peptide drugs, potential immunogenicity concerns
10 may be caused by variations in the API and/or the
11 impurity profile.
12 I'd like to ask Dr. Amy Rosenberg to start
13 off by commenting on available predictive
14 in silico, in vitro, and animal studies to evaluate
15 immunogenicity risks due to impurity or formulation
16 differences and any scientific gaps that will need
17 to be addressed.
18 DR. ROSENBERG: So it's a very interesting
19 area in terms of the word "predictive." So
20 typically, in silico type methods are used in
21 respect of the sequence variations and how those
22 might impact binding to HLA, for instance, and the

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1 consequences thereof. So that's typically how
2 in silico is used.
3 In vitro, on the other hand, is
4 something -- and animal studies, are both
5 critically important in evaluating immunogenicity
6 risk of these kinds of formulation and impurity
7 differences.
8 So I think of this as sort of in a tiered
9 way that you have in vitro studies. You start with
10 in vitro studies that may be meaningful in terms of
11 predicting immune activation. So what are some of
12 those? Cytokine release, perhaps gene expression,
13 and we certainly can think about using
14 next-generation sequencing to look at that rather
15 than the studies and technologies that are more
16 variable.
17 Particularly important, I think, with these
18 kinds of evaluations are also the animal studies.
19 This is mentioned here. So, in vitro, yes, you can
20 do the kind of studies that we just talked about,
21 where you'd get cell lines that express various
22 receptors for impurities, and you'd use those. And

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1 that's a good start. You have the use of cell
2 lines or actually human PBL, which again is a bit
3 more variable, but will give you a potential
4 read-out in terms of differences here. And that's
5 what we're really interested in, differences
6 between the generic and the RLD.
7 But, the ultimate test actually would be
8 animal studies. You can use the inbred strains of
9 mice. You can test the RLD versus the generic, and
10 you can look at parameters of immune responses that
11 are potentially important.
12 So not just do they make an antibody
13 response, but how quickly do they make an antibody
14 response? What kind of antibody response do they
15 make? What's the antibody isotype? Do you get
16 isotype switching? What's the duration? How long
17 does the response last? And so, you know, lastly,
18 does it have hypersensitivity elements to it?
19 So you can look at many aspects of an immune
20 response. Do you develop neutralizing antibodies?
21 There are many, many aspects of an immune response
22 you could look at in these inbred strains of mice

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1 comparing one to another. So, I think that is
2 probably, you know, it is not what people want to
3 go to. We'd like to keep things out of animals.
4 But, nonetheless, I think that can be an amazingly
5 useful tool in addition to the in vitro kinds of
6 studies that we talked about and that Dr. Verthelyi
7 has developed.
8 DR. STRAUSS: David Strauss, the Division of
9 Applied Regulatory Science at FDA. So, I'll start
10 out saying I'm not an immunologist, but we do have
11 some very smart ones in the division. And, but we
12 know that immunogenicity is very important. It can
13 alter the pharmacokinetics in the assays that are
14 used, the ligand-binding assays to determine
15 pharmacokinetics. And it can also alter the
16 pharmacodynamics of drugs. This can have a
17 clinical impact potentially if it's interfering
18 with the drug-binding target.
19 And, I think, going forward, we need to know
20 which types of impurities can cause immunogenicity
21 concerns, and there are different ways we could do
22 this, as we've heard, combining in vitro cell

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1 assays and then moving to in vivo models. We have
2 an effort in our division with human eyes, mouse
3 models that combine a human immune system into the
4 mice and have efforts to use this with large-
5 molecule biosimilar drugs. And this can be
6 expanded to generic peptide drugs as a model that
7 could potentially be used.
8 And, yes, I think there are opportunities to
9 really translate between in vitro, in vivo, and
10 in silico to understand where the problems can be,
11 and then where needed, evaluate specific drug
12 products.
13 DR. ROSENBERG: I would just add to that,
14 that we're well-schooled in the quality attributes
15 that contribute to immunogenicity. And those have
16 been published in guidance, our immunogenicity
17 assessment for therapeutic protein products and our
18 article on scientific considerations for generic
19 synthetic salmon calcitonin products.
20 These are well known, aggregation, the
21 extent of aggregation, the size, et cetera,
22 molecular weights, the deamidation, which we know

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1 facilitates aggregation, oxidation. We're very
2 well-schooled in the kinds of product degradation
3 or post-translational modifications that contribute
4 to immunogenicity. And those really should be
5 those easily measured and the equivalence of those
6 shown.
7 I think particularly important are forced
8 degradation studies. So, you know, the generics
9 should degrade in the same way and the same tempo
10 under the same conditions as the RLD. And I think
11 those studies are critically important for being
12 able to look at the propensity of each product to
13 degrade in a way that would potentially impact
14 immunogenicity.
15 DR. CHOI: Thank you. I'd like to go on to
16 the next proposed priority area, which relates to
17 predictive in vitro bioequivalence methods for
18 long-acting injectables.
19 If Dr. Diane Burgess could start off this
20 discussion by commenting on when an in vitro/
21 in vivo correlation would be necessary for an
22 in vitro bioequivalence determination for long-

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1 acting complex drug products.
2 DR. BURGESS: Sure. So, in my lab, as it
3 was presented earlier, we've been able to establish
4 IVIVCs for quite complex products such as
5 microspheres that have three phase release profiles
6 of a burst followed by kind of a lag phase and then
7 a secondary burst. And we've now been able to
8 establish IVIVCs for this type of complex product.
9 So I think it is important to be able to
10 develop these types of IVIVCs, as they could
11 potentially be used as for bioequivalence studies.
12 I do believe that.
13 So we've been able to do this for different
14 types of drugs in microspheres for more water
15 soluble as well as less water-soluble drugs, more
16 hydrophobic drugs. And I think that the next step
17 here would be to do a bioequivalent study with one
18 of these types of products, maybe with a simpler
19 product like a suspension product, and try to
20 establish an IVIVC for a simple suspension product,
21 and then do the studies in a small-scale human
22 trial on that to prove that our IVIVC is

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1 acceptable.
2 DR. CHOI: Are there any industry responses
3 to this comment?
4 DR. VAITHIYALINGAM: In this regard, what we
5 found is, it was extremely challenging to figure
6 out what happens to a depot injection, for example.
7 If the injection is given intramuscularly, that's a
8 depot injection, and if the injection is expected
9 to stay like a few weeks. So, what happens to the
10 product in this ambience, in the muscular ambience?
11 How do we predict that, you know? How do we create
12 a system or in situ method that would sort of give
13 us an idea of what happens to the product? What is
14 the rate of degradation, or does it settle, or does
15 it stay in the one place? How does it disperse
16 within that site of administration?
17 So we tried a lot of techniques for a
18 particular hormonal long-acting injection, but
19 unfortunately, we couldn't come up with a system or
20 a process that would mimic what happens to the
21 product in the site of administration.
22 DR. BURGESS: So, is that for like a

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1 suspension product, or?
2 DR. VAITHIYALINGAM: Yes. It was a
3 suspension product.
4 DR. BURGESS: A suspension product, right.
5 So, you could use definitely an animal model
6 to look at that, and then you do like a serial
7 sacrifice, and look at the tissue at different time
8 points, and extract from that, and then look at how
9 much has been released.
10 There's also in vitro release testing
11 methods I think where you can simulate that kind of
12 thing by using different solvents, because
13 sometimes the drug may crystallize or recrystallize
14 in that environment, go in to solution, come back
15 out of solution, and there are ways of trying to
16 mimic that also in vitro, I believe.
17 DR. VAITHIYALINGAM: I mean, you are right.
18 We didn't go to the animal models. We just purely
19 went to the in vitro, such as we use the cells, and
20 then we, we sort of created an ambience where the
21 site of administration would be such as the pH,
22 ionic strength, and then sort of what would be a

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1 situation if the drug is given in the muscular
2 compartment.
3 So we created a certain level of in vitro
4 cells, and then we administered the drug. And we
5 kept it for a few weeks then to see what happens to
6 that. But somehow, the results were not sort of
7 tangible or they were not helpful.
8 So, I think there is more research that is
9 needed in terms of what sort of testing ambience
10 should be created to measure what you said, some of
11 the attributes, what I said like sedimentation or
12 degradation, or the other attributes just said,
13 solubilization, crystallization.
14 So, I think a deeper understanding is needed
15 or more research is needed in this area.
16 DR. BURGESS: No. I think you really have
17 to start with an animal model, and then let that
18 drive your in vitro model because just trying
19 initially with an in vitro model, you don't really
20 know what you're doing. And the animal model for
21 the muscle is typically the rabbit hind leg. And
22 it's good, but it's not absolutely ideal because,

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1 typically, you're trying to model the human gluteus
2 maximus, so there are differences there. There are
3 differences in vascularity and movement.
4 Typically, we found that this speeds up
5 release quite significantly in comparing the rabbit
6 model to data that's available in humans for
7 different drug products such as some of the
8 microsphere products like Risperdal Consta.
9 But it is a good model, and you can get a
10 lot of good information from that. And doing a
11 kind of serial sacrifice and looking at the site
12 can give you really a lot of information. Even the
13 technique of injection of some of these products,
14 the suspensions, but also some of the in situ
15 forming gels and so on, like how you inject into
16 that muscular space, can eventually affect your
17 release profile, and so on. So there is an awful
18 lot to be gained from the animal models.
19 DR. VAITHIYALINGAM: Okay. Understood. So,
20 it is just not the in vitro, but you have to couple
21 that with some level of animal studies and clinical
22 studies.

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1 DR. BURGESS: Then you can go back and
2 better design your in vitro model.
3 DR. VAITHIYALINGAM: Got it. Thank you.
4 DR. VELAGAPUDI: I have one comment. This
5 is Raja from Sandoz. The animal models, when we do
6 that, like we held monthly injections, and then
7 three-month injections, six-month injections, you
8 have all kinds of long-term injectables, you're
9 looking at a BE study predicting a BE outcome from
10 the in vitro or animal model. You are talking
11 about individual responses that can detect.
12 So, if you have, like, say, pilot study
13 that's 20 subjects, 15 subjects, or 12 subjects,
14 the responses are varying very much in individual
15 subjects in these long-term injectables. And until
16 you reach to a point of a pilot study of 20 or
17 something, you really cannot get what the meaning
18 is.
19 And, when you use the animal models, you
20 need to have a large number of animals to actually
21 predict what the differences between RLD and test.
22 Unless you have a 10 percent difference in the

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1 mean, you know, like in the formulations, really
2 cannot say that you can go into the humans.
3 So that's where the animal models are
4 getting, like, limited in usefulness. And the
5 in vitro model has to actually predict the
6 long-term ones that can take two months. And some
7 of those things are difficult, and we're going into
8 the animal models where the animal models have to
9 be really large and also have to have a long-term
10 animal studies. And it has to be a large number to
11 detect the differences, at least 10 percent
12 difference; otherwise, it becomes useless.
13 And the other thing we noticed with these
14 things are that with a large animal, like the
15 animal size and the volume of injection becomes an
16 issue. In human, you are injecting large volumes
17 like, say, whatever, you know, 1 mL, whatever, but
18 the same thing you inject into a small animal, that
19 the distributional things will become different.
20 DR. BURGESS: On the last point, the rabbit
21 model is quite good. Small animal models like mice
22 and rats, I agree. But once you get to the larger,

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1 the USDA species, then I think you're okay with
2 that.
3 Also, in the animal models, I think they are
4 easier to control than the human studies, maybe
5 because of the way we keep the animals, house them,
6 the way that we are injecting them, consistently,
7 so we're not seeing such huge variation. And we
8 were able to pick up the differences like in the
9 microsphere formulations that we made that were
10 Q1/Q2 to themselves, but had different in vitro
11 release profiles. We saw exactly the same
12 differences in the animal models. It was terrific,
13 actually.
14 DR. VELAGAPUDI: Can you detect 10 percent?
15 DR. BURGESS: Yes.
16 DR. CHOI: I'd like to go on to our final
17 proposed priority area. FDA is proposing
18 conducting research on characterization of
19 suspension and colloidal products. If
20 Dr. Katherine Tyner could comment on considerations
21 when determining the critical quality attributes of
22 suspension and colloidal products.

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1 DR. TYNER: So FDA has approved colloidal
2 products into this complex bucket, and we actually
3 have over a dozen products that are either IV,
4 ophthalmic, or oral colloids that are suspensions,
5 or colloids that have a product-specific guidance
6 associated with it.

7 And while we always caveat with case by
8 case, and product specific, and my personal
9 favorite, it depends, we can take a look at the
10 products, and we have the ability to generalize and
11 talk about some of the commonalities between these
12 products.

13 In general, the extended testing and the
14 definition of the CQAs is going to be based upon
15 the complexity of the product. So, the more complex
16 you have the product, the more testing and CQAs are
17 going to be needed.

18 First and foremost, if you have something
19 that is a colloid or suspension and has something
20 suspended, there needs to be a fundamental
21 understanding of what is in there and what it is.
22 And that goes for both the intentional and

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1 unintentional particles that are in your system.

2 Hand in hand, we talk about particle size
3 distribution, surface features, composition, and
4 then, when you get to these other routes of
5 administration, morphology, drug release, route of
6 administration, viscosity, and pH, all start to
7 play into these characterizations.

8 Now, the question then becomes how much
9 characterization, to what extent, and with the
10 advancement of these analytical techniques, what do
11 we use?

12 And, so, to that point, we had a comment
13 earlier in the day that it always seems like it can
14 be a moving target in terms of what we're asking
15 for the characterization, the critical quality
16 attributes of these products. But I would propose
17 that instead of a moving target, it's a refined
18 target, and that refining is coming from the
19 science and research that we're doing to advance
20 our knowledge base in this area.

21 DR. ROSENBERG: With regard to particle
22 size, that brings into consideration immunogenicity

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1 concerns, especially for peptides and biologics.
2 For instance, PLGA particles, there was a human
3 growth hormone product that was formulated within
4 particles, and it was much more immunogenic, and
5 so, it was subsequently pulled.

6 So, you get into considerations of
7 immunogenicity depending on particle size, particle
8 distribution, how it's injected, et cetera. So,
9 that's another caveat with regard to particle
10 issues.

11 DR. VAITHIYALINGAM: Specifically for the
12 drugs that have extremely low solubility, the
13 particle size distributions or phase
14 characterization plays a big role. And, if the
15 particles, I mean, if the drug substance or API, if
16 it is a nano-sized material, then the complexity
17 increases even more. Now in the colloidal, this
18 portion where the drug is, is it suspended assays
19 or is it adsorbed within the colloid system? For
20 example, if you take cyclosporine, that is one of
21 the most challenging things, where the drug is,
22 right?

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1 So I think it goes beyond the few things
2 that have been proposed here, particle size, safe
3 surface characterization. I agree that these are
4 the starting points. And as you said, the more one
5 understands the complexity of the product, the type
6 of CQAs that kept increases, it is unfortunate.
7 But the more we understand, then the more we find
8 out which sequence we need to look into.

9 I think the burden is both with the FDA and
10 with industry. So, I think, I agree, these are
11 just starting points. There could be a bucket load
12 of CQAs that come in, depending on what kind of
13 drug product it is.

14 DR. CHOI: I'd like to ask one follow-up
15 question. FDA has a number of product-specific
16 guidances for some of these complex drug products,
17 outlining specific characterization tests.
18 However, there is still a lack of generic drug
19 approvals in this category.

20 Would it be helpful to add more
21 characterization tests or a greater in-depth
22 outline of what these tests should be? In your

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1 opinion, do you think that would help speed access
2 to generic drugs?
3 DR. SRINIVASAN: Nice question, Stephanie.
4 Actually, I'll go back to what Vincent was talking
5 about. I was the reviewer and team leader for the
6 iron for [indiscernible] actually when we approved.
7 And the trick was constant communication.
8 And I think that's something, you
9 know, guidances are great. You guys are doing a
10 great job. But what we are missing is what we
11 could do is pick up the phone and talk and say,
12 hey, I'm not convinced with this; do you think you
13 can do something else?
14 It was a collaborative effort and, you know,
15 the only one with AB rating was passed. It was not
16 just meeting requests, written responses, formal
17 things, but a lot of informal interactions, which
18 led to this, very similar to new drug and, you
19 know, where people go. And a lot of things I'm
20 hearing makes me feel that, you know, having that
21 model would have been wonderful, where people could
22 come and talk and, you know, have a much clearer

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1 idea of what needs to be done rather than just
2 written responses, you know, and formal
3 communications.
4 DR. VELAGAPUDI: I just want to bring one
5 thing on the particle size distributions and the
6 characterization. One thing for everyone, like,
7 should one be looking at the time of the
8 manufacturing versus at the end of stability? Do
9 we have to, you know, follow the characterization
10 at the beginning, at the end of stability studies,
11 or just one is enough?
12 Agency?
13 DR. TYNER: I'm going to actually add on to
14 that, even looking into stability, but also in-use
15 stability tends to be very critical for these
16 products.
17 DR. BURGESS: I guess you would need to look
18 at the product and see what changes you have at the
19 end of the shelf-life stability. And if there are,
20 does it look like significant changes in, for
21 example, particle size or some of the surface
22 characteristics, then, you probably do need to

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1 follow up on that and do animal tests or other
2 tests to find out if those differences are really
3 going to be translated into the in vivo
4 performance.
5 DR. CHOI: So, we will actually have to
6 conclude this panel session and also the first
7 session on complex drug products. Panel members
8 and anyone else in the audience, if you have
9 additional comments, please submit them to our
10 docket.
11 We will now take a 10-minute morning break.
12 Actually, 8-minute morning break. We will resume
13 the workshop in this room at 10:25 a.m. Thank you.
14 (Whereupon, at 10:17 a.m., a recess was
15 taken.)
16 DR. LIONBERGER: So, welcome back, everyone,
17 to our second session. So, the topic for this
18 section is Equivalence of Locally-Acting Drug
19 Products. And we'll begin this session with a
20 presentation from Markham Luke, who's the director
21 of the Division of Therapeutic Performance, the
22 Office of Research and Standards.

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1 So, welcome, Markham.
2 Presentation – Markham Luke
3 DR. LUKE: Hi. Good morning. Good morning,
4 everybody. Welcome to the Food and Drug
5 Administration, ladies and gentlemen, fellow
6 scientists, fellow FDAers. I've been an FDA
7 dermatologist for the last 19 years, and contrary
8 to popular belief, dermatologists don't just
9 prescribe topical products. We do prescribe
10 systemic products, biologics, and a variety of
11 complex, other complex products as well.
12 But, today my job is to talk a little bit
13 about equivalence of locally-acting drug products.
14 And for that, we're going to focus in on what are
15 locally-acting drugs, first of all?
16 These are drug products that are not
17 intended to be absorbed into the bloodstream.
18 Their main site of action is local, like the skin,
19 the mucosal surface of the nose and the lungs, the
20 eyes, the ears. And some of these products that
21 we've discussed do overlap with the prior talk.
22 In the past, FDA has relied on clinical

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1 endpoint bioequivalence studies when there are no
2 other alternatives available. And those studies
3 are difficult to do at times. They can offer
4 require large populations. Sometimes, those
5 populations are the populations of a city if you
6 want to do it properly in some cases. You can talk
7 to our favorite statisticians. They may still not
8 be sufficiently sensitive at times.

9 So, why are we focusing on locally-acting?
10 There are relatively fewer generic products for
11 locally-acting drug products. Of note, the generic
12 products, when we look at the generic products,
13 when we look at the reference list of products
14 without generic products, a good percentage of
15 those are locally-acting drug products. So, we do
16 have to address those difficult-to-get-to-generic
17 products. And because many of those are locally
18 acting, we're focusing on that today.

19 New technologies are available to provide
20 new approaches for generic product equivalence.
21 Just a note there, successful innovation favors
22 when there is a juxtaposition of a usable

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1 technology that's reliable and provides good
2 science together with a need for that either
3 measurement tool or that scientific principle.

4 So, hopefully, we're at that juxtaposition
5 for many of the technologies. And I'm going to
6 discuss a few of the technologies that our Agency
7 has funded to move along the science and some of
8 the audience members and institutions across,
9 around the world who helped participate in the
10 development of this science.

11 So, let's talk a little bit about the
12 regulatory basis for this alternative approach.
13 This is bioequivalence for topical products, which
14 is a drug that's not intended to be absorbed into
15 the bloodstream.

16 It says in our Food and Drug Cosmetic Act,
17 this is the statute, this is where our regulations
18 stem from and our guidances come from those
19 regulations, that "the Secretary may assess
20 bioavailability by scientifically valid
21 measurements intended to reflect the rate and
22 extent to which the active ingredient or

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1 therapeutic ingredient becomes available at the
2 site of drug action." So, we're going to go to
3 where the action is.

4 Just a little bit about topical product
5 formulations. They're heterogeneous, they can be
6 any number of different descriptors. Creams and
7 lotions are common descriptors. I've also heard
8 use of other terms. There have been papers
9 published about what constitute, what are creams,
10 what are lotions. And this is one area that we are
11 actively discussing and investigating.

12 We heard a lot about Q1/Q2, and we're at the
13 verge of the Agency, over the course of the last
14 decade, of bringing out what is Q3, defining the,
15 what a Q3 can encompass different things for
16 different people, but we're trying to come up to a
17 standard approach to this is Q3, and this is what
18 we need to define Q3.

19 So, let's go, for those folks in the
20 audience that are not familiar with the Qs: Q1
21 means the same components; Q2, the same components
22 in the same concentration; and Q3 is the same

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1 components, same concentration, and the same
2 arrangement of the material.

3 This means I'm getting down to the
4 microstructure of what is an ointment, what is a
5 cream, like we saw the picture, and then about
6 spreadability, the look and feel, the water
7 retention, all of those aspects that define the
8 product as used by the patient or the physician
9 prescribing to the patient.

10 Q3 is characterization-based determination.
11 There is in vitro performance data that can support
12 Q3 equivalence while allowing small Q3 differences.
13 And these Q3 differences come from manufacturing or
14 excipient sourcing.

15 But at the heart of the question is what do
16 those Q3 differences mean? Do they matter in the
17 context of bioequivalence? And can we show that
18 they matter? So, these are things that we are
19 thinking of as we move forward.

20 So, FDA, thanks to the GDUFA, had funded six
21 coordinated grants around the world. And this is
22 important, that we've addressed multiple labs

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1 looking at similar science, trying to make sure
2 that they align with each other and that the
3 results are reproducible. We've been looking at
4 new in vivo data. We've been looking at how
5 semi-solids are manufactured with the different
6 formulations, and viabilities in formulations, and
7 how does that result in differences in, say,
8 rheology and differences in the Q3. We've
9 characterized the semi-solid formulations to get at
10 that.

11 We've been looking at new PBPK modeling
12 approaches, and this is in conjunction with our
13 fellow division in DQMM. So, we have a very good
14 collaboration across our office and around CDER.

15 Our goal with this research is to advance Q3
16 equivalence, to get it to the point where we can
17 say this is the way to show bioequivalence. And
18 I'm going to discuss one of the product areas that
19 we have had some success with just this year.

20 I want to talk a little bit about open-flow
21 microdialysis because I think this is getting at
22 the heart of looking at measuring concentrations at

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1 the site of physiological action of the drug. This
2 involves dermal insertion of a semi-permeable tube
3 and measuring the concentrations.

4 I recognize that may be some kinks still
5 need to be worked out with regard to how
6 microdialysis is done, the analysis of the active
7 ingredient concentrations, the interference with
8 other agents in the local milieu. So, all of that,
9 we're working those specifics out. And it could be
10 ready for prime time, but we need to continue to
11 nurture that specific scientific arena.

12 I want to talk a little bit about the
13 acyclovir cream, 5 percent. Those of you in the
14 know or who are FDA guidance watchers have seen the
15 draft guidance come out. The team here, which
16 covered multiple offices across CDER, helped put
17 together this guidance under the leadership of Sam
18 Raney in my division.

19 As you know, we looked at a variety of
20 different formulations of acyclovir cream. We've
21 looked at some of the Q3 aspects, including
22 rheology, including IVRT and also IVPT. We've

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1 looked at the differences formulation can make in
2 particle size. We've also looked at container and
3 closure systems and the impact of that on the
4 crystalline morphology, and hence perhaps the
5 bioavailability of the active ingredient. And from
6 that, we did publish a guidance looking at possible
7 best attributes to think about as you derive an
8 in vitro-only approach for acyclovir cream.

9 I also want to point out some of our
10 research funding went to in vivo dermal
11 microdialysis techniques. This is a picture of
12 someone wired up to look at their local
13 concentrations. As you can see, this is an
14 evolution in the system. This is a portable system
15 now. It's no longer someone stuck to the bedside
16 with a big pump system, and we think this is
17 fantastic. We will continue to explore the limits
18 of what current technology can push.

19 So, this is not a Ferrari. This is moving
20 there in the context of providing good new science.
21 Ferrari is old science, by the way. I think the
22 Honda Civics are more reliable than Ferraris, and

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1 you're more likely to get to where you're going in
2 a Honda Civic. So we would like to say good
3 practical application of science will get you
4 there. And this potentially could be in that
5 direction.

6 We also have done some BE studies with
7 acyclovir cream, 5 percent, looking at dermal PK,
8 20 subjects, and I'm going to go through this
9 quickly. And, the bottom line was that when
10 comparing a U.S. formulation of acyclovir cream, we
11 could detect a difference in a 5 percent
12 formulation. Even though the ingredients were very
13 similar, we were able to discern the difference
14 between U.S. and Austrian-formulated acyclovir
15 cream as opposed to U.S. acyclovir cream compared
16 with itself using this technique.

17 There was some discussion about ophthalmic
18 products earlier. We have grant support from
19 multiple institutions on ophthalmic product
20 characterization, both in vitro drug release, drug
21 delivery modeling. And our division, together with
22 our sister divisions, looked at modeling and

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1 simulation tool chains. We're looking at in vitro
2 release methods from, here example of three
3 different institutions, University of Finland,
4 Texas A&M, and University of Connecticut. So,
5 Europe, red state, blue state, we've covered the
6 spectrum there.

7 Q3 in vitro approach for Q1/Q2 formulations.
8 We've looked at the cyclosporine emulsions,
9 difluprednate emulsions most recently. And we've
10 developed good guidances for these products as
11 well. And hopefully, these have helped bring good
12 products out to market. There are other guidances
13 that we're working on with Q3 approaches, and they
14 are slowly moving on the way.

15 All the inhaled drug products is another
16 area that it's locally-acting. And these are
17 locally-acting in the respiratory tree. With these
18 inhalation products, the research there involves
19 dissolution, particle size, and PK studies.
20 There's various modeling in deposition, and we've
21 been exploring a variety of different possible
22 areas and tools, including radiologic methods,

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1 et cetera. And we're looking at some non-Q1-Q2
2 inhalation products as well and exploring how these
3 products work. There have been 15 product-specific
4 guidances for inhalation products available, and
5 we're gradually working on more.

6 And, as you know, in the setting of complex
7 products in this world, we talk a lot about the
8 weight of evidence. And this is a slide to just
9 remind us briefly what weight of evidence is. It
10 includes device and formulation design.

11 Many of these are combination drug-device
12 products, so, how similar is the device, how
13 similar is the formulation. All those are factored
14 in, in the context of is it sufficiently
15 biosimilar. Comparative in vitro studies are
16 looked at, comparative pharmacokinetic studies,
17 comparative pharmacodynamic and clinical endpoint
18 studies. All these factor into this weight-of-
19 evidence approach.

20 We've published some guidances on
21 applications, and we also have recently published a
22 guidance on device, human factors, as you saw,

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1 there was a draft guidance published earlier this
2 year.

3 We've conducted research coordination for
4 inhaled drugs, everywhere from formulation to
5 device, to human factors, to regional deposition,
6 to dissolution, to absorption. This is one of the
7 fancy types of slides with multiple small pictures
8 that you can barely see. But there, I think it's a
9 cool slide because it covers a variety of different
10 areas that we've covered.

11 So, nasal products, we've used PK studies to
12 look at a variety of these nasal products and
13 comparing with regard to particle sizing. And, the
14 particle sizing tool was first available in 2012,
15 right around the start of our current GDUFA.
16 Seeing that and where it's coming over the last
17 five years as a tool, it's progressed to the point
18 where we feel much more comfortable using this
19 tool. And in 2016, we had an ANDA approved using
20 this technology.

21 So, you can see the evolution of science
22 juxtaposed with the need for that science in the

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1 approval of generic drug products.

2 This is summarizing two different approaches
3 to locally-acting equivalents. And I guess there
4 is some overlap. The Q3 characterization and
5 performance, we discussed earlier, ophthalmic,
6 dermatologic focus, sites for applications direct.
7 There's a key guidance in ophthalmic emulsions,
8 topical ointments that we've provided.

9 ANDAs have been approved based on Q3
10 approaches. These do not allow for Q1/Q2
11 differences, so if you're a different Q1/Q2, you
12 cannot get to Q3 the same. There is a weight of
13 evidence approach, which does allow for some
14 Q1/Q2/Q3 differences, but you're looking at the
15 particle sizes at the site of delivery. You're
16 looking at concentration at the site of delivery.

17 And currently, this is being used for nasal
18 inhalation sites where there's indirect delivery or
19 a delivery device. And these present some
20 challenges for certain active ingredients like
21 inhaled corticosteroids, which we recognize and we
22 continue to work on.

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1 So now, how do you bring those two together,
2 both the Q3 and the more generalized
3 characterization approaches? So, this is something
4 that we're exploring together with our colleagues
5 in the Office of Bioequivalence. How we get there,
6 how these two biometric approaches come together,
7 this is something that we can continue to talk. If
8 industry has opinions -- I know industry has
9 opinions about that -- we're happy to listen to
10 that.

11 So, we're going to have some discussion
12 questions, which Rob is going to lead the
13 discussion questions about gaps in our
14 understanding of locally-acting products and how
15 should we prioritize our future research
16 directions.

17 We're going to look at common themes across
18 locally-acting drugs that might yield useful
19 research targets. And here's a list of some
20 things. These will be presented again in the
21 slides with the questions that are coming.

22 But just briefly, development of

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1 alternatives for clinical endpoints, development
2 for both steroids and nasal products, evaluation of
3 impact of identified differences in user interface
4 for generic drug-device combination products,
5 expansion of characterization-base BE methods
6 across the full space of topical dermatologic
7 products, and expansion of characterization-based
8 BE methods across the ophthalmic products. So,
9 these are all the major focus areas for locally-
10 acting.

11 We have a preeminent panel assembled here,
12 and thank you all for coming. Some of you have
13 come a long distance, and we had some good
14 conversations leading up to this meeting of the
15 minds here. So, ears to you guys. Okay. Rob.

16 Public Comment Period

17 DR. LIONBERGER: Thanks, Markham.

18 Now we'll move to our open public hearing
19 part of this. We do in the future welcome industry
20 perspectives as well, and we did invite the
21 industry to present in this panel as well.

22 So our first open public hearing speaker is

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1 Sid Bhoopathy from Absorption Systems.

2 DR. BHOOPATHY: Thank you. So, we set out
3 to build a tool that can look into both formulation
4 function and maybe the product's intended effect or
5 its postulated mechanism of action. We attempted
6 to do this using biopharmaceutics dissolution, so
7 it is essentially an in vitro dissolution
8 absorption system that combines traditional
9 dissolution testing with a means to determine and
10 quantify interactions with a biorelevant membrane.

11 The biorelevant membrane can do multiple
12 things. It can look at permeation or lack thereof.
13 It can maybe look at up-relation of a relevant
14 biomarker that triggers a cascade of events that
15 eventually results in the PD of the product. It
16 can maybe look at metabolism, and furthermore, the
17 possibility of combining the interplay of
18 metabolism with absorption.

19 So, the early prototypes lacked the ability
20 to introduce a finished presentation. So, we
21 switched it to a dissolution where we popped
22 inserts into it. These are replaceable membranes.

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1 And now, we have the ability to do so much more,
2 and this system has been characterized and
3 validated using multiple media, multiple membranes,
4 and over 20 drug products.

5 So, briefly, I'll touch upon three
6 applications, formulations, full effects, and local
7 GI equivalence.

8 A formulation, the left panel, is where
9 you're using more routine monitoring tools to
10 assess lot-to-lot variability, not as
11 discriminatory. With a simultaneous tool like this,
12 you have the ability to do more. The lower panel
13 is for a BCSIII where a dissolution profile does
14 not show discrimination, and we believe there are
15 multiple gated approaches like this that can do
16 better.

17 Food effect, again, with pharmaceuticals
18 dissolution, without this biorelevance, there is
19 usually an expectation of a direction when you're
20 thinking about BCSII or BCSIV, enhanced solubility,
21 which may be considered, contemplated, or
22 translated into enhanced exposure, not always the

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1 case because there is entrapment, there is
2 biocellular formulation, and so on, that would
3 limit the exposure. And this can look into both
4 such attributes.
5 Now, I want to close with PK and local GI
6 equivalence. PK, at least in our experience so
7 far, this has better scalability. So the rate of
8 permeation increased can better correlate to maybe
9 a change in Cmax versus a 300 percent increased
10 dissolution that has less in vivo translatability.
11 And when you do not have permeation and
12 you're trying to assess a local effect such as
13 biomarker upregulation, a simultaneous device like
14 this results in a much smoother performance or
15 potency profile. And this has widespread
16 application. There are 10 GI products where we see
17 its potential utility or 5 billion in sales, and
18 about a million patients impacted, so this requires
19 your collective support. Thank you.
20 DR. LIONBERGER: Our next open public
21 hearing speaker is Dr. Vinod Shaw.
22 DR. SHAH: Thank you. And I appreciate the

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1 opportunity to give this presentation about the
2 classification of topical drug products, a way
3 forward to reduce the regulatory burden. The
4 concept of topical drug classification has already
5 been published in 2015-2016, but to provide a
6 brief, the topical classification is a framework
7 for classifying the topical drug products based on
8 the qualitative and the quantitative composition,
9 Q1/Q2, and the microstructure arrangements of the
10 matter, and the in vitro release.
11 TCS when applied will help in approval of
12 the generic topical drug products without
13 conducting the in vivo studies, but assuring
14 product safety and efficacy.
15 The drugs are classified into four different
16 classes as you can see it here. Topical
17 classifications within class 1 where the product is
18 Q1, Q2 and Q3. Q3, again, is the microstructure,
19 but we determined the in vitro release. And in
20 most of the cases, including the microstructure, we
21 have found that it correlates with the in vitro
22 release of the dosage form.

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1 So, that would be the class 1, which would
2 be eligible for biowaivers. And the class 3, which,
3 again, the Q1/Q2 are different, but the Q3 is the
4 same, and that can be eligible for biowaivers.
5 Whereas class 2 and class 4 where Q1/Q2 is the
6 same, but Q3 is different, microstructure is
7 different, it would be class 2. And when
8 everything is different, it would be class 4, and
9 that would not be eligible for the biowaiver.
10 This classification is almost analogous,
11 similar to the well-known classification of the
12 biopharmaceutics classification system, which was
13 established almost about 20 years ago. Yet, as you
14 can see, for class 1 and class 3 BCS, you can get
15 the biowaivers, class 2 and class 4, you cannot.
16 They had to do the BE studies, whereas the same
17 thing is true for the topical drug classification
18 systems.
19 Right now, we have prepared 12 different
20 formulations with the changes in the manufacturing
21 process or the composition to the products in the
22 classification of BCS I, II, III. We will be

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1 conducting the in vitro release, in vitro
2 percutaneous penetration, Q3 arrangement,
3 microstructure arrangement, rheology, and also we
4 will be conducting the pilot BE studies using the
5 DPK.
6 So, what I would like to propose and
7 indicate and request the Agency to invite them to
8 collaborate our efforts and to support the present
9 work, which may facilitate the evaluation of the
10 potential use of the BCS in the development of
11 topical products and the regulatory evaluations.
12 This will definitely facilitate the generic
13 product development. It will reduce the regulatory
14 burden and assure the product quality across all
15 therapeutic classes, availability of the topical
16 drug products to patients and consumers at a more
17 reasonable cost. Thank you for your attention.
18 (Applause.)
19 DR. LIONBERGER: So, our next speaker is
20 Vatsala Naageshwaran from Absorption Systems.
21 DR. NAAGESHWARAN: Thank you for this
22 opportunity. The focus of my presentation is to

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1 highlight how complex biology can augment
2 formulation characterization and strengthen the
3 scientific framework for assurance of equivalence.
4 So, there are numerous barriers for complex
5 ophthalmic generic product development, and
6 regulatory initiatives to include Q3 as an in vitro
7 option for a subset of products is a step in the
8 right direction. However, this is still very
9 product specific and key questions about
10 sufficiency of this approach still remain.
11 So Q1/Q2 formulations do not always have the
12 same physical-chemical properties as we are all
13 aware, and this type of chemical complexity can be
14 elucidated through structural analysis and in vitro
15 release testing.
16 However, formulations which meet the
17 specified parameters can still have very different
18 biological properties in terms of permeability,
19 accumulation, distribution to target issues,
20 efficacy, and even safety. And therefore, there is
21 a requirement to elucidate biological complexity to
22 address this residual uncertainty.

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1 So a lot of comparative studies to look at
2 the underlying biology, which is based on a
3 comprehensive understanding of the RLD is required
4 to provide a basis for equivalence of biological
5 properties.
6 So this needs to be integrated along with
7 the physical-chemical characterization, and this
8 type of strong scientific evidence is of efficacy
9 and safety is what will provide confidence to the
10 clinicians.
11 Ophthalmic drug products, unlike other
12 pharmaceutical products, do not require human PK
13 data as part of the approval because target ocular
14 tissues and even surrogate tissues like aqueous
15 humor cannot be sampled serially.
16 Even in the post-approval life cycle of a
17 drug product, human PK data is not obtained.
18 Instead, there's reliance on pre-clinical models
19 whose ocular compartments resemble human and
20 validated in vitro models which have established
21 IVIVC.
22 So whether this is a model that looks at

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1 dilution and stability in tear film, or permeation
2 across a corneal conjunctive or scleral tissue
3 surface, or distribution to target tissues like
4 iris ciliary body, or efficacy within a disease
5 model where you're looking at quantitative
6 endpoints like reduction in IOP, this integration
7 of this data, you know, provides this basis for
8 comparing equivalence of the biological properties
9 that can be integrated with the physical-chemical
10 characterization that Q3 provides. And further, it
11 must be noted that there is IVIVC because these
12 tests generate data for the RLD, for which you have
13 human efficacy data.
14 So in conclusion, integration of various
15 data parameters from physical-chemical
16 characterization as well as biological
17 characterization provides a performance matrix that
18 gives us a deep understanding of a complex product
19 and its process. Thank you.
20 DR. LIONBERGER: Thanks very much. Our
21 final open public hearing speaker is Lisa Parks,
22 representing the Association for Accessible

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1 Medicines.
2 DR. PARKS: I am Lisa Parks, vice president
3 of sciences and regulatory affairs at the
4 Association for Accessible Medicines, AAM. AAM
5 represents the manufacturers and distributors of
6 generic pharmaceuticals.
7 Generic pharmaceuticals represent greater
8 than 89 percent of all prescriptions dispensed in
9 the U.S., but account for only 27 percent of
10 expenditures on prescription drugs, saving
11 patients, payers, including the U.S. government,
12 nearly \$5 billion a week.
13 Today's generic industry includes a range of
14 diverse companies who have become global leaders
15 both in providing safe and effective medicines and
16 pioneering nearly new treatment options for
17 patients. Generic competition continues to play a
18 vital role to improve access to pharmaceuticals and
19 driving cost savings to the American patients and
20 healthcare system.
21 This growth in the generic industry has led
22 to the creation of thousands of jobs across the

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1 country and improved the quality of life for untold
2 millions of people. AAM engaged in GDUFA II
3 negotiations to continue building on the foundation
4 laid by GDUFA I, which increased access by
5 improving timeliness and predictability in the ANDA
6 review process.

7 One of the fundamental pillars of GDUFA was
8 to improve communication and transparency between
9 industry and FDA. We've learned from GDUFA I that
10 it's not just during the ANDA review where
11 increased communication and transparency were
12 needed; rather, effective communication and
13 transparency earlier on in the R&D process is
14 critical in increasing the quality of submission
15 and therefore first-cycle approvals. Industry and
16 FDA captured this key point in GDUFA II.

17 As FDA continues its work, its good work, in
18 the regulatory sciences, it must also keep dialogue
19 with industry open. AAM has stated in the past
20 that quality is a two-way street. FDA must be
21 vigilant in keeping the communication pathways
22 between FDA and industry open and strong.

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1 Industry has a wealth of real-world
2 experience it can share with FDA as FDA develops
3 guidances and other tools to assist industry in
4 increasing the quality of applications. FDA has a
5 tremendous mission of ensuring safe and effective
6 products are available to patients.

7 Industry will do its part in submitting the
8 highest quality ANDAs, but FDA must do its part in
9 reviewing those ANDAs in a consistent manner in
10 order for all of us to succeed and have a
11 successful program.

12 We applaud the Agency and OGD for holding
13 this interactive public workshop, and we implore
14 you to continue open communication and transparency
15 with industry to ensure increased access to safe,
16 effective, and affordable generic medicines. Thank
17 you.

18 (Applause.)

19 Panel Discussion

20 DR. LIONBERGER: Thank you, Lisa. So that
21 now concludes the open public hearing, and we'll
22 move to our panel discussion. So to begin our

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1 panel discussion, we'd like our panelists to
2 introduce themselves and their affiliation, and
3 we'll start with Badrul.

4 DR. CHOWDHURY: My name is Badrul Chowdhury.
5 I am the division director of the Division of
6 Pulmonary, Allergy, and Hematologic Products in the
7 Office of New Drugs. Thank you.

8 DR. COOK: Denise Cook, medical officer,
9 dermatology. I am in the Division of Dermatology
10 and Dental Drug Products in OND.

11 MR. DiLIBERTI: Charlie DiLiberti,
12 independent consultant with Montclair
13 Bioequivalence Services.

14 DR. HAVAPURNHAL: Ravi Havapurnhal, senior
15 vice president at Amneal Pharmaceuticals. Also, I
16 have to say I'm former FDA. Thank you.

17 DR. HOCHHAUS: My name is Guenther Hochhaus
18 with the University of Florida.

19 DR. LEE: Sau Larry Lee, deputy director
20 from Office of Testing and Research in the Office
21 of Pharmaceutical Quality.

22 CMDR NGUYEN: Commander Josephine Nguyen,

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1 dermatology, United States Navy, associated with
2 Uniform Services of Health Sciences, USHS,
3 currently a Robert Wood Johnson Health Policy
4 Fellow in Congress.

5 DR. PETERS: John Peters, deputy director,
6 OGD.

7 DR. RANEY: Sam Raney, the scientific lead
8 for topical and transdermal drug products within
9 the Division of Therapeutic Performance, which is
10 in the Office of Research Standards in OGD.

11 DR. YIM: Hi. Sarah Yim, director of the
12 Division of Clinical Review in the Office of
13 Bioequivalence in OGD.

14 DR. LUKE: Hi. Markham Luke, director of
15 Division of Therapeutic Performance in the Office
16 of Research and Standards in generic drugs.

17 DR. LIONBERGER: Alright. So, to begin the
18 discussion, before we dive into some of the
19 different locally-acting routes of delivery, I want
20 to start with some discussion about the drug-device
21 combination products, several of which are locally-
22 acting.

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1 We'd like the panel to address some of the
2 complexities that they see in the development of
3 the review of these products and identifying any
4 areas for research that can potentially help FDA
5 identify how to develop and review these products
6 more efficiently.

7 DR. LUKE: Hi. Markham Luke. I know that
8 we have a variety of products that have a need for
9 generic products that are combination products, and
10 these are combination device and drug products.

11 The device is an inherent part of these
12 products and can sometimes make it difficult to
13 have a bioequivalent product because of the way
14 they're designed. And I think we have some folks
15 on the panel with companies that might have
16 interest in these products and may want to talk a
17 little bit about those.

18 And right now, many of these have certain
19 clinical attributes. We've published a draft
20 guidance looking at human factors with regards to
21 possible concerns about the user interface and
22 whether and looking at the threshold analysis, what

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1 sort of studies would address some of the threshold
2 analysis pieces that are vital to evaluating the
3 bioequivalence of these products.

4 DR. LIONBERGER: Ravi?

5 DR. HARAPANHALLI: Thank you for this
6 particular topic. I think it's very near and dear
7 to many generic companies. I would say that the
8 guidance that was published is really a great first
9 step. It really talks about risk-based evaluation,
10 threshold analysis, and the exterior designed
11 features that the user has to interface with
12 between the RLD versus the generic and how to go
13 about assessing that. I think it's well thoughtful
14 guidance, and it certainly helps a lot.

15 A few points. So the implicit meaning in
16 that guidance and also what we're discussing here,
17 it points out that there can be situations where
18 design features may be different in a generic
19 combination product than the reference product.

20 So as long as, you know, everybody agrees
21 that there can be some difference, it may be born
22 of design features. It may be most of the time

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1 born of restricted intellectual property claims
2 that many innovators have claimed.

3 There are many devices where over 200 claims
4 have been filed for certain devices by the
5 innovators, and it's a humongous task for generic
6 companies to really navigate through all this maze
7 and to come with their design that best represents
8 the innovator's product in terms of usability
9 design features and patient acceptance, while all
10 the time ensuring the critical quality attributes
11 for the device are preserved, and maintained, and
12 are equivalent to the reference product.

13 So keeping that in mind, I feel that
14 building off this guidance, as long as companies
15 are able to differentiate certain exterior features
16 and justify why they believe that those features do
17 not significantly change the IFU for example. Maybe
18 it's part of the initial threshold analysis, but
19 maybe followed by some focused human factor
20 assessment. Maybe it's a usability study all the
21 way escalating to a formal human factors study.

22 So as long as those features are identified

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1 and focused on these studies and it's shown that
2 despite those minor differences, devices are
3 equally accepted and used by a patient population,
4 I think that should really serve the purpose here.

5 DR. LUKE: You didn't mention so the issue
6 of whether the differences are minor or not might
7 have differences with regards to the indication or
8 the use of the product. And I know that Dr. Peters
9 here has thought a little bit about that area.

10 Do you want to comment on that, John?

11 DR. PETERS: Sure. Somehow, I knew you were
12 going to do that. The problem is made considerably
13 more difficult because of the significant changes
14 in practice of medicine and practice of pharmacy
15 over the last 20 or so years, where the patients no
16 longer get as much training with device drug
17 combinations.

18 So the corollary, the therapeutic corollary
19 to Murphy's law is that if you gave a patient a
20 particular device drug combination and they could
21 potentially misuse it, they will misuse it. So for
22 that reason, we have to be very cautious in terms

<p style="text-align: right;">Page 137</p> <p>1 of what kinds of differences are allowable, 2 thinking in terms of not only how they might work 3 well, but also in terms of the failure modes of how 4 they might be misused or inappropriately used such 5 that they will fail because of that. 6 DR. CHOWDHURY: Maybe I can comment on this 7 from the perspective of inhalation dosage form and 8 perhaps also injectors. And it becomes complicated 9 when you go across devices. For example, in the 10 inhalation dosage form area, there are broadly two 11 classes. One is metered dose inhalers, you just 12 press and breathe. The other one is dry powder 13 inhaler. 14 Now, for the press-and-breath metered dose 15 inhalers, the instructions for use are pretty 16 straightforward. You press, drug comes out, you 17 inhale. So in that area, the device interface 18 probably would not matter much. An expectation 19 would be the instructions for use for an innovator, 20 and a copy would be more or less the same if you 21 introduce some of the complexity changes such as 22 auto-inhaler mechanisms or some other complexities.</p>	<p style="text-align: right;">Page 139</p> <p>1 for example, if it's an auto-injector for life- 2 saving situations, if it's anaphylaxis, you 3 probably would not want a copy of an innovator to 4 have a different activation mechanism such as one 5 by a press and another one is by a pressure of a 6 button. A patient going through anaphylaxis would 7 probably not be able to use them. 8 In a situation for a chronic use, every week 9 you inject for whatever the disease be you may 10 allow it if you allow the risk-based judgment, but 11 it becomes very tricky because, as we just heard, 12 if patients are given the choices to make mistakes, 13 they actually can make mistakes. Thank you. 14 DR. LIONBERGER: Thanks. 15 So let's move on to our next topic, which is 16 looking into topical dermatological products. And, 17 you know, Markham outlined the characteristics of 18 expanding the characterization-based equivalence 19 approaches, so we welcome some discussion on this. 20 And I think to start the discussion I'm first going 21 to ask some of our -- we have a range of 22 dermatologists on the panel -- some about the</p>
<p style="text-align: right;">Page 138</p> <p>1 In the dry powder inhaler area, these are very 2 different. Each and every one of them has 3 different unique characteristics of how you 4 activate, how you inhale, how you prime for the 5 next dose. 6 So in those areas, I think given what we 7 just heard from Dr. Peters, I think the aim 8 probably would be to have the instruction for use 9 for the innovator and the generic be the same so 10 patients can walk out with no training and go 11 between the two devices and use it without any 12 failures. 13 So that's the expectation. It kind of leads 14 into the trap, if you would, copy of dry powder 15 inhalers with complex design features may be very 16 complicated. So that's why I think OGD needs to 17 comment on the thing, would you allow variations on 18 a risk-based approach. It is a risky place to get 19 into, but if one is willing to get into, one can 20 get there. 21 I think the general sense would be it may be 22 a risky venture. And going into auto-injectors,</p>	<p style="text-align: right;">Page 140</p> <p>1 physical-chemical characteristics that are 2 important to the patients. So if you can comment 3 about which of those attributes, really, we should 4 be looking for, for similarity in terms of patient 5 substitutability of topical dermatological 6 products. 7 DR. LUKE: I have two dermatology colleagues 8 here, Denise Cook and Josephine, and we'd want you 9 all to chat first about this, if you can. 10 DR. COOK: Well, I think Denise Cook. I 11 guess what would be important to patients in terms 12 of topical drug products in general, is that 13 they're easy to use, that they absorb fairly 14 easily. They don't have to spend a lot of time 15 trying to get the product to actually disappear on 16 the skin surface. 17 So I think that the vehicle that the drug 18 product is in is important for compliance for 19 patients. 20 CMDR NGUYEN: As a medical dermatologist, I 21 agree. Having the patient -- actually, it's 22 interesting -- for men, the vehicle is more</p>

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1 important because they don't like to use the greasy
2 things; but for women who want to get the problem
3 resolved quickly, the greasy formulations are
4 actually more impactful and effective because they
5 penetrate the skin barrier more quickly.
6 So, having the patient, so when I approach a
7 patient, I have them understand the formulation,
8 which one's more effective, but which one is also
9 more easy to apply for the work day, especially for
10 military members, they, it's hard to apply an
11 ointment on and then put a uniform on because the
12 ointment messes up their uniform.
13 Another important point is recognizing that
14 skin barriers are different, specially, so you have
15 a normal skin barrier and in many of our patients,
16 like eczema patients, you have a compromised skin
17 barrier. So when you apply a medication on a
18 compromised skin barrier, because there's a break
19 in the skin barrier, the medication can penetrate,
20 oftentimes penetrate more quickly. And therefore,
21 you can actually have blood levels of that
22 medication. For example, in patients with eczema,

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1 severe eczema, studies have shown that application
2 of a calcineurin inhibitor like Protopic, they were
3 found to have elevated blood levels of that.
4 DR. LUKE: Just synthesizing from the two
5 other dermatologists on the panel, the formulation
6 of the product is important clinically because it's
7 appreciated differently by different patients, and
8 hence, vary the numerous types of formulation. And
9 that makes, I guess, our job more difficult and
10 that we have to have more formulations that we
11 would address for Q3.
12 That's differences in the formulation, we
13 have to get them as close as possible to the cream,
14 but in itself, that look and feel of the cream
15 should match the reference product. That's what
16 I'm hearing. So if you're prescribing a cream,
17 that patient is going to get something that is
18 going to be that would need expectations to that
19 regard.
20 DR. LIONBERGER: Ravi?
21 DR. HARAPANHALLI: I think, Markham, your
22 summary of basically two approaches, I think it

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1 makes a lot of sense, Q3 characterization and
2 performance approach versus totality of evidence
3 approach and maybe a combination of two in reality
4 that may be out there.
5 But the point here is that, yes, I think
6 expanding the characterization-based methods or to
7 clearly honing in on the Q3 aspect using various
8 approaches, be it microanalysis, open flow,
9 in vivo, or technique, all those combined, I think
10 it would provide us a good picture of what
11 different toolsets may be available for companies
12 to really pick and choose for their particular
13 product and show that they have a totality of
14 evidence based on all these complimentary methods,
15 in vitro approaches, to show bioequivalence to
16 these topical products.
17 DR. LUKE: Right. Now, the notion of the
18 chemical-physical characterization of the product
19 is key there. For example, that Austrian cream
20 that was studied, if you look at the viscosity of
21 that cream, it's more like a lotion, and it behaved
22 physical-chemically more like a lotion. So in that

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1 essence, you were studying a lotion versus cream
2 even though it was labeled cream.
3 And this was an issue that -- I know, Vinod,
4 you raised classification, but the heart of
5 classification for dermatologic products is not
6 Q1/Q2/Q3; it's what is a cream, what is a lotion?
7 And there have been numbers of papers out there
8 describing those specific product characteristics
9 and what makes a cream a cream, what makes a lotion
10 a lotion, and how similar do they have to be to
11 fall within those characteristics.
12 And to get to a Q3 product, how similar,
13 what gradation of lotion is sufficient to that a
14 patient would not be concerned that they're getting
15 something different from what the original intent
16 that the prescribing physician was.
17 DR. COOK: Denise Cook again. Also, I think
18 how similar the vehicle is to the innovator product
19 is important in terms of efficacy of the drug
20 product because we have found that, depending on
21 the vehicle, it also influences how much the actual
22 drug product either stays in the skin or is wicked

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1 away into the bloodstream.
2 And so whether the product is an ointment,
3 where that actual vehicle may hold it in the skin
4 longer, versus a lotion, which might allow more
5 systemic absorption, is important, and whether any
6 of the other ingredients include absorption
7 enhancers, et cetera, may actually change the
8 efficacy of the drug product.
9 DR. LIONBERGER: John?
10 DR. PETERS: I think just as an observation,
11 it sounds like we're really talking about two
12 separate tracks here. One is in terms of the way
13 that the drug is delivered being an equivalent
14 fashion, and the other is patient acceptance.
15 Patient acceptance was what we had started
16 with in the discussion, and there are other things
17 that were not mentioned. For example, the
18 sensation that the product gives to the skin. Is
19 it cold? Does it burn? Does it sting? The scent?
20 Those are also things that would be important to
21 patients.
22 So we need to have a little bit of an

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1 understanding also in terms of what were the
2 critical elements for which the patient was willing
3 to continue to use the RLD so that we can design
4 the generic in a similar fashion.
5 MR. DiLIBERTI: Just to follow up on your
6 points and clarify that a little bit. Two key
7 aspects to topical derm products that we really
8 don't assess very well is, A, what dose are we
9 giving? You know, if two products feel different,
10 the patients may be giving effectively a different
11 milligram dose.
12 And number two is, do they stay where we put
13 them? We go to great pains to assess the adhesion
14 of transdermal products, patches and the like, and
15 yet, we really don't do the same for topical derm
16 products. And some products may flake off, they
17 may rub off, much more easily than others.
18 I think if we were to address these critical
19 performance features, we may be able to get away
20 from doing clinical endpoint studies.
21 DR. LIONBERGER: To continue the discussion
22 here, you know, I think we feel very comfortable

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1 that if we have a Q3, Q1/Q2/Q3 formulations,
2 they're going to be matching up all of these
3 physical-chemical attributes. So I think looking
4 forward to research frontiers, let's talk about
5 what we need to do to expand possibilities beyond
6 Q1/Q2/Q3.
7 So, some of the aspects of this that we may
8 want to talk about are the in vivo studies. Are
9 they more needed for non-Q3? Are some of the
10 performance attributes that Charlie mentioned
11 needed? And maybe from industry, some of the
12 challenges is being Q1/Q2/Q3 a barrier to early
13 generic competition?
14 So I'd like to have some discussion about
15 some of the challenges of what would it take to get
16 to a non-Q1/Q2 in a substitutable generic product
17 in the few minutes we have remaining for this
18 topic.
19 So perhaps the industry perspective is, is
20 this something worth doing, right? Or are you
21 happy with an environment where the only non-
22 clinical endpoint bioequivalence pathway for

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1 topical products is being Q1/Q2/Q3? Is there value
2 in having a wider space of formulations available?
3 DR. HOCHHAUS: Just define what you meant
4 when you were saying non-clinical.
5 DR. LIONBERGER: I mean any kind of
6 non-clinical endpoint bioequivalence study. So
7 many of our guidances now are pretty general, but
8 they have a clinical endpoint bioequivalence study
9 that often very large --
10 DR. HOCHHAUS: So a pharmacodynamic one?
11 DR. LIONBERGER: Right, an alternative,
12 right, to say --
13 DR. HOCHHAUS: I believe very, very much in
14 the power of pharmacokinetics also for topical
15 applications. And that was one of your comments
16 where you said you don't know what dose would be
17 applied or what dose would stay on the skin.
18 So I totally believe that the combination of
19 very well-selected in vitro assays and a PK study
20 for those kind of formulations probably can give
21 you the answer whether a generic is equivalent.
22 DR. LIONBERGER: Charlie?

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1 MR. DiLIBERTI: Yes. We always have to be
2 cognizant of what the innovator side of the
3 industry does in response to bioequivalence
4 regulations. And if you require Q1/Q2, then the Q1
5 and Q2 are going to get patented. And we need to
6 have ways of circumventing that in a way that will
7 not affect patients, that you'll still get a safe
8 and efficacious product that's equivalent to the
9 brand, but not necessarily exactly Q1, Q2, maybe
10 close.

11 DR. LUKE: I think there are certain things
12 that are going to be difficult to patent like the
13 Q1 concentration of the active ingredient,
14 switching around the excipients and the like, but
15 yielding a similar Q3 or a similar look and feel
16 could be achievable potentially by substituting
17 certain excipients.

18 The notion of different looks and feels
19 leading to different dosing is an important issue.
20 And a patient like Dr. Peters pointed out, if it's
21 irritating, or stings, or something, or it becomes
22 very goopy, then there's an incentive for the

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1 patient to apply less, and therefore dose less, and
2 hence, the variability in topical dosing.

3 Denise and I reviewed countless topical
4 dermatologic product studies in the new drug arena,
5 and one of the things that we measure is the use of
6 the product. We actually weigh empty tubes with
7 those new drug products and look at how much dosing
8 was actually given to the patient in the context.
9 And that range of dose could be huge depending on
10 what the product is and the relative extent of the
11 disease that the patients have.

12 All of that is difficult. There're
13 multiple, there're more variables. Even though the
14 location of what you're treating is smaller, there
15 are a lot more variables inherent in the
16 application of this pharmaceutical product, of
17 these pharmaceutical products.

18 But at the same time getting at
19 measuring -- we have this really cool tool that we
20 are looking at, this microdialysis. They're
21 looking at the local concentrations. And I saw
22 that there was a discussion in an ophthalmic arena,

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1 too, so this is something that could be probably
2 looking at the relative concentration of the drug
3 at the site, a putative site of action. And that's
4 a valuable, a very valuable tool that we can do
5 comparisons with.

6 So does it matter that you can put more drug
7 on it? You still achieve the same concentration
8 despite putting twice the amount.

9 DR. LIONBERGER: Okay. To finish this topic,
10 we have Larry, Sam, and Josephine. Okay?

11 DR. LEE: Yes, Rob. I think maybe OGD is
12 needed to look into some sort of user study to, not
13 just for this type of product, to really to see how
14 to evaluate how the patient or user feels about the
15 non-Q1/Q2 type of a formulation. I think this is
16 the area you guys may need to look into from the
17 generic perspective.

18 CMDR NGUYEN: Charlie's point of dosage is
19 very important, but it's also important to
20 recognize that skin site location also impacts the
21 penetration. For example, thinner skin, eyelid,
22 it's going to penetrate a lot quicker than thicker

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1 skin on your scalp or on your lower legs.

2 DR. RANEY: So the question of non-Q1/Q2
3 products and just ensuring high quality generics
4 become available, there are a lot of generics out
5 there -- or actually, let me state it a different
6 way. There are many products for which there
7 aren't generics out there despite the fact that
8 there are no patents and exclusivities.

9 Those can scientifically be addressed by
10 Q1/Q2/Q3, we think, because we systematically could
11 address failure modes relating to bioavailability
12 and failure modes relating to patient perception of
13 quality. Does the cold cream feel the right way?
14 Does it burn? Does it sting? Those failure modes
15 can be addressed.

16 Now, as you were speaking about Charlie, at
17 a point in time where you're dealing with a patent
18 restriction to being able to perform that, is it
19 possible to have a very similar Q3 with a different
20 Q1/Q2? That's very possible.

21 The question then becomes how do we mitigate
22 the risk of those failure modes that, historically,

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1 we've evaluated clinically in saying, yes, we know
2 it's efficacious and we know it's well tolerated.
3 Well, pharmacokinetics, I agree with you,
4 has played a large role in making oral solid oral
5 dosage forms bioequivalent and generics available,
6 so that's one approach that we already have
7 interest in, whether it's dermal microdialysis or
8 even epidermal procedures with wicking or
9 spectroscopic techniques.
10 Are there other techniques out there other
11 than perhaps a combination of dermal or cutaneous
12 pharmacokinetics methods, combined with an
13 understanding of the dosage form, which may not be
14 Q1/Q2, but still satisfies or addresses these other
15 failure modes? Are there other techniques out
16 there, that you're aware of, that we could be
17 looking at for these non-Q1/Q2 products?
18 DR. LIONBERGER: I think in the interest of
19 time and coverage, we'll move on to our next topic.
20 Further comments, please submit them to the docket.
21 And we'll have some additional discussion, I think,
22 in our modeling and simulation topic because I'm

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1 going to ask questions about deconvoluting PK data
2 in that session as well.
3 So let's move on to talk about inhalation
4 products. So in inhalation products, the context
5 is a little bit different. In the topical
6 products, we have the Q3 approaches and you say,
7 well, how can we expand them?
8 I think the question is a little bit
9 different for inhalation products. With inhalation
10 products, we have some more general weight-of-
11 evidence guidance out there that aren't limited to
12 Q1/Q2 formulations. But I think here, the
13 challenge may be that the studies that we're asking
14 are quite burdensome and challenging studies. So
15 here, the scientific challenge is not just getting
16 guidance out there, but moving towards more
17 efficient guidance based on strong scientific
18 principles.
19 So I formulated here the question about
20 alternatives to the clinical endpoint BE studies
21 that are currently part of the weight of evidence,
22 but I'd like to open this up for some discussion

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1 around the inhalation area and looking at our
2 guidances in ways that they can maybe be made more
3 efficient, leading toward more access to generic
4 drugs. So maybe we'll start off with Guenther.
5 DR. HOCHHAUS: I have a relatively
6 simplified way of looking at inhalation and
7 bioequivalence. And so for myself, one needs to
8 answer three questions. One is, is the dose it
9 gets in equivalent? Does it stay in the lung for
10 the same period of time? And are the regional
11 depositions about the same, central versus
12 peripheral? And if all those three questions can
13 be answered with yes, if the generic is about
14 similar, then I think it's a good generic product.
15 Now, it's very, very difficult to answer all
16 of those questions. And that is one of the reasons
17 why the FDA says you have to do a clinical endpoint
18 study. But the problem with the clinical endpoint
19 studies is that, at least for some of the
20 drugs -- and corticosteroids are probably one of
21 the problem cases -- there's hardly any dose
22 response curve.

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1 So if there's no dose response, if I even
2 cannot distinguish between 100 and 150 microgram, I
3 would also not be able to distinguish between a
4 product that is more centrally or more peripherally
5 deposited because --- and even any studies that
6 show that clinical endpoint studies can catch that
7 with marketed products -- you maybe can show it
8 with very defined size products. But, so there is
9 a problem.
10 The other problem is that those clinical
11 studies, at least for corticosteroids, I think the
12 number of subjects that you need are around, I
13 don't know, 800,000 or so. So they are very, very
14 expensive. And I can see the dilemma that the FDA
15 is in because there will be certainties from non-
16 generic companies' arguments coming, well, you need
17 to show that they act the same way.
18 But I see maybe two developments. One would
19 be the next one, where we can just say let's maybe
20 try to move from those FEV1 studies to studies that
21 may be similarly designed, but use less subjects,
22 for example. And one might be able to go back to

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1 ENO using the study design that you use right now
2 for FEV1 so that you don't do dose-ranging studies,
3 but just use one dose, use ENO, which has less
4 variability. And then maybe you can get the same
5 result, probably also not showing a very strict
6 dose-response curve, but the result would be there.
7 You would have done a clinical study. I think that
8 could be an intermediate way.
9 The next step I think is really to try to
10 get rid of those clinical endpoint studies and use
11 in vitro studies, which have been shown to have
12 clinical relevance, and to use PK studies that can
13 answer quite a number of those two questions that I
14 started with.
15 It can certainly detect the dose that gets
16 into the lung. It will detect differences in how
17 long it will stay there. And hopefully, we'll be
18 able to show also, at least for some of the drugs
19 that dissolve very slowly, that also PK can pick up
20 differences in central-to-peripheral ratio.
21 But I think in combination, good in vitro
22 studies and PK long term might be a viable way of

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1 showing bioequivalence for this kind of --
2 DR. LIONBERGER: So, I'll follow up on the
3 PK question. So, you know that in the European
4 approach, they rely a little bit more on PK
5 studies, but I think you've seen articles in the
6 literature that talk about batch-to-batch
7 differences in pharmacokinetic studies in the
8 reference products. And that's been a long-
9 standing challenge for the generic industry. What
10 if my batches of the reference product come out
11 different in my test?
12 DR. HOCHHAUS: That's not only a problem
13 with PK, that's also a problem with clinical
14 studies. That's a general problem of those batches
15 that the innovator has come up with. There might
16 be different designs and you might have to
17 certainly think about PK study designs that look at
18 different batches of the innovator.
19 DR. LIONBERGER: Badrul and then Charlie?
20 DR. CHOWDHURY: There are lots of things
21 being discussed. I'll just try to be brief and
22 maybe have some more people weigh in on this. On

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1 the question about alternates to FEV1, I think we
2 have to acknowledge, FEV1 is very much truly
3 tested, accepted endpoint. In situations where it
4 works, it works very well. So that is not
5 necessarily the problem.
6 If one has to look or looking to develop
7 alternates to FEV1, probably some sort of biomarker
8 kind of endpoint, which has been tried, and one can
9 keep on looking for it. I don't think that really
10 is the block of developing generics.
11 The one question we should step back and
12 think about is how much clinical evidence do you
13 need to show sameness? It goes back to what
14 Guenther said. And I would say in many situations,
15 probably one would not need to.
16 For example, in solutions, historically, one
17 has relied on in vitro and not thought about
18 needing a clinical study. It has been done in the
19 past. Drugs have been approved, although there may
20 be some changing course even in the solution area
21 for steroids.
22 Now, for suspensions, you cannot

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1 characterize in vitro. I think the challenge there
2 is more trying to characterize in vitro rather than
3 try to do a clinical endpoint. And in some
4 solutions, the science is lost.
5 So my preference would be really to get out
6 of for the purpose of showing equivalence,
7 clinical, but rely on in vitro, PK or some other
8 methods.
9 Now, another which was brought up is many of
10 the paradigms does not apply equally across
11 inhalation dosage forms. So we're trying to fit
12 the same paradigm for all the initial inhalation
13 dosage forms -- MDIs, DPIs, nebulizers. They are
14 not the same.
15 For MDIs, we got away with that because
16 MDIs, if you all know, the propellant was close to
17 100 percent of the total delivery volume and
18 weight. However, the chlorofluorocarbons CFCs are
19 very, very uniform, so you didn't really have
20 problems in characterizing those. You didn't need
21 to.
22 When you get into the dry powder area, these

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1 are complex dosage forms, and there are actually
2 biologic products in there, lactose. So
3 dose-to-dose variability comes in, and you just
4 cannot apply the MDI standards to DPI. It will not
5 work.
6 So I think one of the research areas that
7 one may want to look at the OGD side is trying to
8 characterize the innovator product before setting
9 out what our bounds would be. Because if you raise
10 a bound for equivalence and test true batches of
11 the reference product and they cannot pass with
12 each other, that's an impractical standard.
13 So I think in some other areas, it just come
14 up, like in the PK highly variable reference, just
15 come up. In the biologic worlds, in the
16 biosimilars, the different products just come up.
17 So this is something of a research area to look
18 into, it's that for complex dosage forms the same
19 standards would not apply. Some different
20 standards need to develop. It's not the problem of
21 the endpoint; it's a problem with the standards.
22 Another, which is complex here to get

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1 into -- I'll just touch on and then leave out -- is
2 we all know, all 85 percent of the products in the
3 U.S. are generics. The problem is patients often
4 complain, and they find differences, which are not
5 there.
6 So it is patient acceptance, and I think it
7 will become gradually heightened because, on the
8 OND side, the Cures Act as we implemented it, and
9 patient preference and patients' outcomes are part
10 of the development paradigm. So this is another
11 challenge to get into the initial dosage form,
12 which applies all across. It's what to do with the
13 patient perception of taking the MDI or DPI and not
14 simply liking it. And if they don't, they'll find
15 a difference. Thank you.
16 DR. LIONBERGER: I think we have Charlie,
17 Larry, Sarah.
18 MR. DiLIBERTI: Very quickly, if you can
19 detect product and lot-to-lot differences with a PK
20 study, that's a much better metric than a clinical
21 endpoint study. I would bet a million bucks that
22 those lot-to-lot differences would never be

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1 detected in a clinical endpoint study.
2 Secondly, for the general class of inhaled
3 corticosteroids, these drugs tend to be very
4 insoluble and slow to dissolve. So in general, the
5 rate-limiting step of the drug going from the
6 crystal inside the alveolus to the central systemic
7 circulation is the dissolution rate in the lung.
8 So therefore, systemic PK is actually a very good
9 measure of local drug action at the lung wall.
10 DR. LIONBERGER: We'll come back to you,
11 Guenther. Larry?
12 DR. LEE: Sorry, Guenther, I go first.
13 But I think I agree. I'll keep it really
14 short. I think we really need to look at the
15 advances, the scientific advances in the inhalation
16 area, especially from the particle engineering,
17 device design, as well as the in vitro because I
18 believe that we actually understand those much
19 better nowadays, and that in fact, we probably know
20 the variability-wide, where the variability coming
21 from the PK in connection to the in vitro
22 characteristics.

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1 So I think in this, at least from my
2 perspective, I think we have much better
3 understanding from the in vitro. I think we should
4 give a little bit more weight on the in vitro
5 finding.
6 DR. LIONBERGER: Sarah, then Guenther?
7 DR. YIM: So I just wanted to briefly say
8 this is a big public health need in my opinion.
9 I'm still educating myself on the nuances and
10 complexities of these issues, and I know there must
11 be a lot of them; otherwise, we'd have a lot more
12 inhaled corticosteroid generics, especially in the
13 DPI area.
14 So I'm not going to wax philosophic on the
15 details, but I agree that we need alternatives to
16 clinical endpoint BE studies. They're just very
17 burdensome and expensive. So that's why we're
18 here, and I'd like to hear more detailed ideas from
19 the subject matter experts. Thank you.
20 DR. HOCHHAUS: I just, I fully agree with
21 your statement, that it's not only burdensome and
22 expensive, it's also the clinical endpoint

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1 strategy, at least for corticosteroids, as Charlie
2 also said, you will not be able to differentiate
3 between dose differences that you would otherwise
4 feel as significant.
5 What Rob just said with respect to
6 comparison of the FDA approach compared to the EMA
7 approach, I think a weight-of-evidence approach
8 using different tools at the same time is very
9 important. And the use of in vitro plus PK
10 certainly will give you much, much more information
11 than just doing a PK study when the in vitro
12 studies fail.
13 In addition, we can also look for additional
14 in vitro studies. And we just said that the
15 regulating step of, might be the dissolution. And
16 I think it's a very, very good idea that we look
17 into the area of dissolution rates in the area of
18 inhalation drugs, to use that as an additional
19 endpoint, an additional point to potentially look
20 for differences between generic and innovator.
21 DR. LIONBERGER: Ravi?
22 DR. HARAPANHALLI: Yes. I want to touch

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1 upon Badrul's point that a generic device may or
2 may not be acceptable by a patient because they're
3 used to a design. And that connects back to John's
4 point earlier that there could be misuse scenarios.
5 But the point here is that, typically, a lot
6 of human factor assessment goes on. Generics don't
7 suddenly come up with their device and say this is
8 it. A lot of development goes on. They are
9 developing their own device, and they are also
10 comparing with their innovators, and formative
11 studies, summative studies, all that goes on.
12 When we talk about misuse and risks, it
13 should be related to risk. It doesn't mean that an
14 innovator doesn't have any risk. They have their
15 own risks, too. So when we compare that risk
16 versus this risk, you should be putting that
17 perspective, and then decisions should be made,
18 whether a generic should be approved or not.
19 And whether somebody likes it or not, let it
20 be left to the market. So once all the things are
21 addressed and it's deemed to be equivalent, then
22 let the market play it out, whether somebody likes

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1 that design or not. So thank you.
2 DR. LIONBERGER: Any further comments on
3 inhalation products?
4 DR. LUKE: The issue of biomarkers, I think,
5 we have -- especially with these, with drugs that
6 work in more chronic fashion. Is there room for
7 that? And also, radiologic studies, looking into,
8 there have been tremendous leaps and bounds on
9 software analysis of a variety of radiologic
10 images. Is that another reasonable approach to
11 looking at, maybe making FEV studies better and
12 less variable in their outcome?
13 DR. CHOWDHURY: I can probably just touch on
14 this a bit. I think people are very interested in
15 developing biomarkers, and there are actually many
16 that are being used in different investigative
17 settings.
18 The problem that comes up is that, it
19 doesn't look like these biomarkers are yet a very
20 sensitive measure of a corticosteroid effect that
21 one can pick up in a clinical setting as a
22 potential difference.

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1 Eosinophil counts have been looked at in the
2 past, investigated extensively, and did not seem to
3 pan out that well. Exhaled nitric oxide, which was
4 at some point a fashion to go after, I think OGD
5 did a very nice study trying to look for those
6 differences, it did not pan out the [indiscernible]
7 either.
8 Now there is some interest in moving out of
9 the human lungs in our division, lung
10 situations [indiscernible] measure resistance and
11 flow in their setting. And those are also
12 alternate approaches to look for.
13 So I think there's interest in biomarkers,
14 but it's not yet there to pick up differences. So
15 I really go back to see if there is any ways of
16 using less of clinical for declaring sameness and
17 if those can be addressed in vitro. We seem to be
18 progressing, as we heard earlier, a bit faster.
19 Thank you.
20 DR. PETERS: I'd like to go back to one
21 thing that Badrul said earlier. As we look at
22 these products, we have to keep in mind that some

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1 of them are for prevention, some are for symptom
2 control, and some are life saving.
3 So from the standpoint of public health,
4 it's our duty to be sure that there are no
5 significant differences that would put patients at
6 risk because that's the point of the public health.
7 So putting something out with a statement
8 like, "Let the market decide," is not going to be
9 something that would really be doable by us. We
10 would have to be assured that that risk-benefit
11 ratio is the same as it is for the RLD. And that's
12 part of the program that we have with generic drug
13 surveillance now, is being sure that we learn more
14 about exactly what are those significant
15 differences in a risk profile as well as in the
16 efficacy profile.
17 DR. CHOWDHURY: I would like to touch on to
18 that. That's a very important point that often
19 gets actually lost. The human factors studies are
20 very useful, absolutely necessary and should be
21 done. But for some life-saving situations, where a
22 patient is to use the drug, you cannot replicate

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1 that in a human factors study.
2 For example, simply an MDI if it works
3 perfectly well if you put it straight out,
4 vertical, and use it, it works. However, if you
5 put it at an angle, it does not deliver. It's very
6 difficult to pick it up. In vitro can pick it up.
7 Human factor may or may not.
8 The person is waking up in the middle of the
9 night, short of breath, and goes for the inhaler.
10 If he cannot use it, ends up in a bad situation.
11 And lying down using it horizontally, if the drug
12 is not going to be delivered, he just can't accept
13 that.
14 So these are very complex situations, and I
15 fully agree that it needs to be looked at in a very
16 detailed fashion. We don't want to put out
17 something which may be potentially life threatening
18 if not used properly or the patient is thinking
19 using properly, but the device features doesn't
20 allow the drug delivery properly.
21 DR. LIONBERGER: The last comment from
22 Sarah.

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1 DR. YIM: Then circling back a little bit to
2 question 1 and acceptable design differences and
3 the issue of substitutability, I think this all
4 sort of ties in because as hopefully we get more of
5 these combination products out on the market, the
6 more tweaks we're seeing in design differences out
7 there, the more substitutability issues might
8 arise, right, where it won't be necessarily patient
9 preference that's driving what device they get.
10 It's going to be what's on the formulary, what's on
11 the formulary that month, things like that.
12 So it gets to be kind of a complex issue,
13 how much differences are you going to actually
14 start allowing in the combination products that are
15 going forward for the generic combination products?
16 DR. LIONBERGER: Let's change topics. A
17 little bit, talk about a different product category
18 and talking about ophthalmic products. And here
19 again, a question for the panel, moving toward in a
20 similar way to the topical products, expanding the
21 space for ophthalmic product characterization.
22 So again, ophthalmic products are

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1 regulations, so they have to be Q1/Q2. So that's
2 off the table. But we heard discussions from Bob
3 Bellantone this morning about in vitro release
4 tests, that if you have a good release test, you
5 might be able to say well I have a Q3 difference,
6 but it's acceptable because it meets an important
7 model of product performance.
8 So I'm interested in a discussion on the
9 ophthalmic product category.
10 MR. DiLIBERTI: All right. I'll start. So
11 let's talk not about the emulsion formulations, but
12 about the suspensions, simple suspensions, drug
13 crystals in an otherwise clear liquid.
14 I'm not sure what you gain by any human
15 studies on those beyond what you already find
16 in vitro. You can characterize those as well as
17 anything else. And to me, to do a rather onerous
18 aqueous humor PK study seems a bit over the top.
19 DR. LIONBERGER: Larry?
20 DR. LEE: Yes. Rob, I think this is a good
21 idea, but I think the key question -- maybe OGD in
22 the future wants to look at it if you do decide to

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1 go to the in vitro route -- you try to have a more
2 systematic approach to decide to determine what is
3 the full orthogonal set of in vitro
4 characterization you need to do in order to
5 demonstrate Q3. I think there is a different way
6 to do it.
7 One way is you have to understand the
8 relationship between the manufacturing as well as
9 certain attributes, changes in certain attributes.
10 So I think this is the area that you may want
11 to -- I recommend OGD will probably want to look at
12 it if you want to decide to go forward using an
13 in vitro approach.
14 DR. LIONBERGER: Let's take it to a little
15 bit about the suspension characterization of the
16 suspension products. Are there any scientific gaps
17 that would prevent us knowing attributes of
18 ophthalmic suspensions that are clinically
19 relevant?
20 DR. LUKE: I just want to point out that
21 when you discuss the full space of ophthalmic
22 products, and the folks in the ophthalmic group

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1 would agree, that it encompasses products for use
2 in any part of the eye, including the area around
3 the eye, some of which is skin, or lash, or hair.
4 And what is your target organ or target tissue is
5 going to vary depending upon what your product is,
6 what your formulation intent is.
7 So if your target is the hair roots, and
8 you're trying to grow lashes, versus the use of the
9 product to affect the iris or looking at
10 intraocular pressure management, those all have
11 different target organs and may require different
12 approaches to looking at both clinical B from what
13 we've seen and also perhaps penetration of the
14 product into this space where the site of action
15 is.
16 DR. LIONBERGER: Also interested in comments
17 on -- you've talked about both dermatological and
18 ophthalmic products. Both sometimes have semi-
19 solid products that have similar characterizations,
20 some have suspension products.
21 So are there common themes that we can learn
22 across the Q3 characterizations that can be

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1 generalized? Would there be interest from the
2 industry in more general guidance on Q3
3 characterization that would help that in general?
4 So we're open to comments on that. What
5 could FDA do to help generalize these Q3 approaches
6 across a broader range of dosage forms than just
7 one product-specific guidance? So Larry first.
8 DR. LEE: I think one thing you may want to
9 look at is the ability to characterize certain
10 particles in the mixture environment. I think, for
11 example, let's say you want to determine particle
12 size in the presence of other excipient. How are
13 you going to do that? I think that is something
14 that from the analytical perspective, you may need
15 to overcome some of these challenges.
16 DR. LIONBERGER: Charlie?
17 MR. DiLIBERTI: I think suspension, simple
18 suspensions where it's just drug crystals in an
19 otherwise clear liquid, are low-hanging fruit here.
20 I think we have easily the analytical technology to
21 characterize those incredibly well. So I would
22 recommend focusing on those.

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1 DR. LUKE: I would say, for the ointments
2 and the creams that are used around the eye, a very
3 similar approach we are taking for dermatologics
4 could be applied. Essentially, once you
5 characterize a cream, and we haven't had the tools
6 to do so, I think we can apply them across the
7 panoply of those products.
8 DR. LIONBERGER: So we have about five
9 minutes left, so I want to just tee up a few
10 final -- and give you the opportunity for one last
11 comment in this area. Some things we haven't
12 covered and talk about potentially are for nasal
13 products, and if you have any specific comments and
14 some similar issues related to I think the
15 inhalation areas, where we have outlined weight-of-
16 evidence approaches.
17 There may be an opportunity to move toward
18 more characterization-based approaches for the
19 nasal products or just any other attributes of the
20 locally-acting products that you think we should
21 consider in terms of our research activity.
22 So it's a pretty broad comment, and I open

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1 for the final comments.
2 DR. CHOWDHURY: In a broad sense, for the
3 nasal product, the same thing that we discussed for
4 the inhalation product applies. And just to keep
5 in mind, at least for the inhalation, there's an
6 FEV1. For nasal, there is no FEV1. The situation
7 for a clinical endpoint is actually even worse.
8 Therefore, the need for depending on an in vitro
9 probably is even a bit more. Thank you.
10 DR. LIONBERGER: Guenther and then Larry?
11 DR. HOCHHAUS: I almost could repeat exactly
12 what I said for the inhalation studies. The
13 clinical endpoint for nasal studies is, again, so
14 weak, there is no dose response. I think it's even
15 written in the guidance that there's no dose
16 response.
17 So why do a clinical study where you even
18 can't distinguish between doses and make companies
19 go through that hurdle?
20 I see some possibility of maybe improving
21 in vitro tests. Dissolution would be one
22 possibility also for nasal space, then use PK as

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1 the in vivo measure of exposure.
2 DR. LEE: If I remember correctly, the
3 reason we use a clinical endpoint study for nasal
4 spray is because of our inability to characterize
5 the particle size in the nasal suspension. I think
6 the times have changed a little bit. I think an
7 analytical perspective, where you start to have
8 some analytical method, that may be capable of
9 doing this. So I think we definitely should
10 consider this type of a method in your
11 bioequivalence approach for nasal products.
12 DR. LIONBERGER: Charlie?
13 MR. DiLIBERTI: I agree 100 percent with
14 getting rid of clinical endpoints, that is, for
15 nasal products. But on the in vitro side, we need
16 to seriously revisit the types of tests that we
17 require, and what the criteria area, and what their
18 clinical relevance is.
19 One case in point is ovality ratio. Does it
20 really matter? And I've seen companies struggle
21 for months and months to try to get this test to
22 pass.

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1 DR. LUKE: We also want to address spray
2 pattern. Is that right?
3 MR. DiLIBERTI: Yes. You calculate an
4 ovality ratio. It's basically an ellipse in the
5 major to minor access ratio. And companies just go
6 crazy over this. It doesn't mean anything because
7 it's measured at a much longer distance than the
8 spray would ever reach inside the nasal passages.
9 DR. LIONBERGER: A lot of these questions
10 about how significant these are, how to interpret
11 different in vitro tests, how to interpret PK
12 studies, one framework for handling that is through
13 understanding models of skin absorption, lung
14 deposition, nasal absorption.
15 So we want to cycle back to that in our
16 fourth session today about how we use the
17 absorption base models to help us make decisions
18 around some of these improvements in the
19 locally-acting products.
20 So with that, we've reached the end of our
21 morning session. We'll reconvene at 1:00. I hope
22 I said that right. And again, if you pre-ordered

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1 lunch, it will be available at the kiosk. There's
2 also lunch rooms. If you go out the hall and
3 behind here, there are rooms with tables set up for
4 lunch. You don't have to sit in the hallway,
5 although it is a quite nice day, and there is an
6 outside park as well outside the doors there as
7 well.
8 So we'll be back at 1:00. Thanks, everyone.
9 (Whereupon, at 11:59 a.m., a lunch recess
10 was taken.)
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1 AFTERNOON SESSION
2 (1:00 p.m.)
3 DR. LIONBERGER: Welcome back, everyone, to
4 our afternoon session. The topic for Session 3 is
5 Therapeutic Equivalence Evaluation and Standards.
6 And everything that we're not talking about in any
7 of the other sessions fits into this category.
8 So to provide the introduction, I'd like to
9 introduce Myong-Jin Kim. She's the deputy director
10 of the Division of Quantitative Methods and
11 Modeling in the Office of Research and Standards.
12 So welcome, M.J.
13 Presentation – Myong Jin Kim
14 DR. KIM: Thank you, Rob.
15 My name is Myong-Jin Kim. I also go by M.J.
16 in case it's hard to pronounce my name. I hope you
17 really enjoyed the weather outside during the lunch
18 hour. It's one of the most gorgeous days that we
19 have ever seen recently.
20 So I'm here to give you some FDA research
21 update for the therapeutic equivalence evaluation
22 and standards. For my talk, I'm going to talk

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1 about three topics, which is general bioequivalence
2 issues for systemically acting drugs, the
3 biowaivers and predictive dissolution methods for
4 solid oral products, and lastly the equivalence of
5 modified-release products, including abuse-
6 deterrent formulations.
7 Sorry, I forgot. As you know, abuse of
8 opioid drug products is a serious public health
9 concern, so one way to mitigate the safety concern
10 is to develop opioid drug products that are
11 formulated to deter abuse.
12 Because it is important that the
13 availability of generics does not exacerbate the
14 public health problems associated with prescription
15 opioid abuse, sponsors should demonstrate that a
16 generic solid or opioid product is no less abuse
17 deterrent than its reference product with respect
18 to all potential routes of abuse.
19 In March 2016, FDA issued draft guidance for
20 evaluating AD of generic solid oral opioid
21 products. However, although publishing a guidance
22 has opened the door for generic competitions, as of

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1 May 2017, there are no approved ANDAs for generic
2 AD opioid drug products. On the other hand, there
3 are 10 new drug products with AD properties that
4 have been approved, one recently approved in late
5 April 2017.
6 So in terms of finalizing the draft
7 guidance, based on the comments that we received
8 from October 2016, FDA opioids public meeting, and
9 the comments submitted to the FDA docket, our
10 guidance revision effort is ongoing, and we expect
11 that the guidance will be finalized by November
12 2017.
13 While significant progress has been made to
14 finalize the guidance, we feel that research is
15 still needed to make generic drugs available. The
16 research objectives for generic AD formulations are
17 to bridge scientific gaps in generic guidance for
18 evaluating generic AD solid or opioid drug
19 products.
20 This can be done by identifying optimal
21 in vitro and in vivo methods for evaluating generic
22 AD opioid products at the formulation, physical,

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1 and chemical manipulation, PK and PD levels. In
2 terms of standardizing in vivo evaluation of the AD
3 properties, nasal PK studies, oral chew and oral
4 crushed PK studies, and nasal PD studies for
5 AD-formulated products containing aversive agents
6 can be considered. For in vitro evaluation,
7 extractions, syringeability, and sublimation
8 studies are important to consider.
9 This slide shows you the ongoing research
10 efforts from the FDA on generic abuse deterrence of
11 opioids. Two research projects, contracts,
12 pertains to evaluation of drug product formulation,
13 in vitro performance characteristics related to AD
14 of solid oral dosage forms of opioids, and a PK
15 study of AD opioid drug products following
16 insufflation of milled drug products.
17 For internal collaboration, the in vivo
18 predictive method for determining opioid
19 bioavailability following chewing of solid oral
20 opioids and regional deposition fraction
21 quantification and dissolution testing of nasally
22 insufflated OxyContin using an in vitro method are

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1 currently ongoing.
2 We are also working to develop an IVIVC of
3 chewed versus intact Hysingla tablets using
4 in vitro drug-release base on the simulated chewing
5 method. In addition, PBPK and PK/PD modeling and
6 simulation efforts of nasal insufflation and oral
7 routes of opioids are ongoing.
8 For future research considerations, two
9 research areas are of our interest, human
10 insufflation PK studies and PD products containing
11 aversive agents. For abuse by insufflation, it
12 should be noted that all current AD reference
13 products have AD labeling related to abuse by
14 insufflation in the nasal route.
15 Currently, there's no established in vivo
16 predictive in vitro method, and the draft guidance
17 recommends in vivo PK studies for the nasal route.
18 With these in mind, research is needed to
19 understand the critical attributes such as particle
20 size and the role of polymeric excipients, as well
21 as manipulation methods to prepare the test and the
22 reference products for insufflation PK studies.

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1 With respect to AD products containing
2 aversive agents, it should be noted that aversive
3 agents are not generally listed as active
4 ingredients, and thus, generic products may have
5 different aversive agents than the reference drug.
6 Given that the draft guidance recommends a
7 comparative PD study, if test product contains
8 different aversive agents or less amount of the
9 same aversive agent, we would like to hear from the
10 panel if there are any alternative approaches that
11 can be used to evaluate generic ADF with a
12 different aversive agent from the reference
13 product.
14 Now, shifting the gear to the current issues
15 in BE for solid oral dosage forms, we are faced
16 with the following questions when evaluating the BE
17 assessment of generic drug products. When is the
18 PK profile similarity needed for BE? What are
19 additional assessments for partial AUC or
20 similarity in Tmax?
21 Do we need tighter BE limits for certain
22 products?

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1 Is in vitro dissolution reliable for
2 regulatory decision-making about BE?
3 As RLD labels expand to include more
4 information about specific populations, methods of
5 administration, or drug interactions such as those
6 with proton pump inhibitors, do we need more
7 in vitro or in vivo BE data?
8 In terms of utilizing partial AUCs as BE
9 evidence, there may be different approaches for
10 applying the use of partial AUC in the BE
11 assessment. However, the underlying basis is that
12 there is a clear PK/PD relationship that shows a
13 clinically significant sensitivity to PK
14 differences.
15 For example, early partial AUC can be
16 assessed for a quick onset of effect while later
17 partial AUC is to evaluate the sustained drug
18 release. Additionally, partial AUC can be used to
19 evaluate the similarity of drug release throughout
20 the GI tract.
21 Another issue in BE for solid oral dosage
22 forms is whether a tighter BE limit is needed for

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1 some drugs such as those with a narrow therapeutic
2 index. As you know, NTI drugs have a small
3 exposure window where they are both safe and
4 effective. Therefore, BE standards should be risk
5 based, and they should allow less variations for
6 these NTI drugs.
7 Another set of questions is, is in vitro
8 dissolution reliable for regulatory decision-making
9 about bioequivalence? For evaluation of
10 dissolution differences, modified release products
11 with formulation design differences such as
12 comparing the operable matrix release mechanism
13 against the osmotic pump-based release mechanism or
14 the post-approval product quality investigation
15 that no dissolution differences, may pose a
16 challenge in terms of how to reliably use these
17 findings for regulatory decision-making.
18 As I mentioned earlier, RLD labels often
19 expand to include more information about specific
20 populations, method of administration, or drug
21 interactions.
22 For example, a reference product label may

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1 describe how this drug can be administered via
2 enteral tube administration, and a risk of clogging
3 may have been studied under certain specific
4 circumstances, or it may describe a drug
5 interaction with proton pump inhibitors where these
6 drug interaction findings can affect the drug
7 released that is based on a pH-dependent mechanism.
8 In order to ensure the same level of safe
9 and effective use of generic drugs as the reference
10 product, the question is, do we need more in vitro
11 or in vivo BE data?
12 One approach to address these issues in BE
13 assessment for solid oral dosage form is to utilize
14 a modeling and simulation method. Dr. Liang Zhao
15 will represent a quantitative method in the
16 modeling approach in support of the GDUFA
17 regulatory science research program in more detail
18 in a later session of this public workshop.
19 But briefly, FDA uses modeling and
20 simulation, and virtual BE simulations to examine
21 these cases to guide regulatory standards.
22 Sponsors are encouraged to utilize these modeling

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1 and simulation tools in support of proposing
2 alternative BE approaches.
3 While the PBPK model approach is often used
4 in the new drug development arena, this approach
5 can support the regulatory decision-making for
6 generic drugs as well. They range from
7 identification of clinically relevant specification
8 of in vitro tests such as dissolution and risk
9 assessment for new formulations with release
10 mechanism changes; BE extrapolation from healthy
11 volunteers to specific populations; waiver of
12 in vivo studies using virtual BE simulations; and
13 assessments of effects of PPI on drug exposures,
14 especially for formulations that are pH dependent.
15 In addition to PBPK, the quantitative
16 clinical pharmacology approach is useful BE
17 assessment of solid oral dosage forms. Its impact
18 can range from PK matrix determination for BE such
19 as evaluation of partial AUC, model-based BE
20 assessment, and BE study simulations.
21 This slide shows a list of some research
22 projects, and they range from NTIs, PBPK for

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1 systemic and locally-acting products, to
2 model-based BE assessment for PK and performance.
3 Dr. Liang Zhao will go over these in more detail in
4 his presentation.
5 With all this in mind, for our panel
6 discussion, we would like to hear from you how we
7 can integrate predictive dissolution, PBPK, and
8 PK/PD models for decision-making about generic drug
9 BE standards and what would help to reach this
10 goal.
11 Let's shift gears to our last topic, BCS
12 class 3 drugs and biowaiver for solid oral
13 products. In May 2015, FDA published a revised
14 guidance for waiver of in vivo BA/BE studies for IR
15 solid oral dosage forms based on a BCS. This
16 guidance includes biowaiver extension to BCS
17 class 3 drug products.
18 As you know, biowaivers can be granted for
19 highly soluble and highly permeable drug substances
20 in IR solid oral dosage forms that exhibit rapid
21 in vitro dissolution. For BCS class 3 drug
22 products, in order to be qualified for a biowaiver,

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1 the drug substance should be highly soluble, and
2 the drug product is very rapidly dissolving. In
3 addition, BCS class 3 test drug products must
4 contain the same excipients as the reference
5 product.
6 The composition of the test product should
7 be qualitatively the same and quantitatively very
8 similar to the reference product. This is due to
9 the concern that the excipients can have a greater
10 impact on the absorption of less permeable drugs.
11 This objective of eliminating the need for
12 unnecessary in vivo BE studies. Extension of
13 biowaivers to BCS class 3 drugs was included in the
14 guidance as stated in the GDUFA 1 commitment
15 letter. However, there is a concern that the
16 current BCS guidance on class 3 waivers is not
17 helpful to the generic drug industry because most
18 generic solid oral products use different
19 excipients than the reference product.
20 I have listed several research ideas here,
21 and we would like to hear from the panel how we may
22 expand BCS class 3 waivers to non-Q2 formulations.

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1 With this in mind, we do have three priorities for
2 the panel. One is in vitro alternative to in vivo
3 nasal studies for abuse deterrence of solid oral
4 dosage form of opioids.
5 The second one is how do we integrate the
6 predictive dissolution, PBPK and PK/PD models for
7 decision-making about generic drug bioequivalence
8 standards. And lastly, how do we expand BCS class
9 3 waivers to non-Q2 formulations?
10 DR. LIONBERGER: Thanks very much, M.J.
11 Our next speaker is representing the generic
12 industry, so this is Siva Vaithiyalingam. He's
13 from Cipla, and welcome, Siva.
14 Presentation – Siva Vaithiyalingam
15 DR. VAITHIYALINGAM: Thanks very much, Rob.
16 I appreciate it.
17 Good afternoon, everyone. My name is Siva
18 Vaithiyalingam. I am from Cipla Laboratories, and
19 many of the discussions, many of the things that I
20 wanted to speak of have already been covered by
21 M.J.
22 Thank you, M.J. You did a great job. Thank

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1 you, Rob, for your introduction and bringing me
2 here.
3 Before we started on this project, M.J. and
4 I had a good discussion, and we had four different
5 topics to talk about. The first one was
6 essentially, the abuse-deterrent products, opioids.
7 The second one was on the partial AUC. The third
8 was on the BCS 3 regs. And the fourth one was the
9 NDA drugs. So these are the four topics,
10 essentially, we discussed about the talk in this
11 workshop.
12 The first one was on the abuse-deterrent
13 opioids. And currently, as M.J. said, there is a
14 guidance, but the guidance is primarily focused on
15 the new drugs. As of now, the guidance is focusing
16 more on the new drugs. So what we really want is
17 pretty clear, something for the generic drugs.
18 In the typical abuse, the product is
19 crushed, snorted, injected where the drug is
20 available for systemic circulation in a rapid
21 manner in a high intensity. So with that in mind,
22 there is not much of hope in the guidance to the

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1 generic industry in terms of how to develop, or
2 perhaps most importantly how to test to the point
3 where the generic product is as abuse deterrent as
4 the reference, which is the key, isn't it? Apart
5 from being equivalent orally, it has to be as good
6 as the abuse deterrent.
7 So I think, from that perspective, perhaps
8 our request is to have a good amount of research
9 focused on establishing the conditions,
10 establishing the tests that are required for
11 demonstrating the sameness in the abuse-deterrent
12 potential between both reference and test.
13 Essentially, I'm summarizing what I said.
14 In the research areas need to be focused to the
15 extraction procedures that mimics the real-world
16 techniques that folks use to extract the product,
17 extract the API from the product. And then the
18 endpoints, the extraction procedure sometimes is so
19 long, they do end it.
20 So that kind of information would be really
21 helpful. The guidance would be really helpful for
22 the industry.

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1 The next topic is on the partial AUC.
2 Partial AUC is a really challenging thing for
3 establishing the bioequivalence evidence. On many
4 occasions, what we've found is that the guidances
5 are out in a very late stage, so the first and the
6 foremost thing that we request is the guidances on
7 partial AUCs to be on a timely basis.
8 Secondly, we request the agency to put a lot
9 of resources on sound scientific principles in
10 terms that the PK profile and partial AUC should
11 completely correlate with the therapeutic outcome
12 in the patients. If these things are not
13 considered perhaps as you would easily imagine, BE
14 metrics, which is the partial AUC for certain
15 drugs, may cause a significant generic barrier.
16 The third topic that I wanted to speak is on
17 the BCS 3 waiver. In BCS 1 compounds, at least we
18 have a good grip on it in terms of the biowaiver.
19 And I'm very glad that the agency is looking into
20 BCS 3 waiver also. However, as M.J. pointed out,
21 the major obstacle in this BCS 3 compound is
22 ensuring qualitative and quantitative sameness for

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1 the criteria of establishing the BE criteria.
2 I think the reason for requiring a
3 qualitative and quantitative sameness is the
4 underlying principle of excipients can somehow
5 enhance the permeability. But in reality, what we
6 found is a majority of the excipients, with the
7 exception of mannitol and other permeation
8 enhancers -- at most 99.9 percent of the excipients
9 that we use in the IR and ER products, they almost
10 have no impact on the permeability of the API.
11 On that basis, perhaps our fear is a blanket
12 requirement of qualitative and quantitative
13 sameness can cause a significant regulatory
14 barrier. Therefore, our request is to put a lot of
15 effort in figuring the class of excipients in terms
16 of which class of excipient we should avoid or
17 which class of excipient -- if the RLD has, then
18 the test drug should have the same class of
19 excipients; so some sort of a leeway instead of
20 having a blanket requirement of QQ.
21 It boils down to specifically figuring out
22 the mechanistic understanding of permeation

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1 enhancers and the structural activity relationship.
2 That comes to the next topic of narrow
3 therapeutic index drugs. As such, for the narrow
4 therapeutic index drugs, we have very strict
5 requirements in terms of assay and blend uniformity
6 and content uniformity test.
7 This narrow therapeutic index, for example,
8 if you take levothyroxine or warfarin, even the
9 manufacturing process has to be so robust and
10 rugged, we have to meet very tight CMC criteria
11 such as assay, blend uniformity, and content
12 uniformity. And in addition to that, we have very
13 strict requirements for bioequivalence.
14 So our request is, perhaps there is a list
15 already that has been published by FDA, which are
16 all the NTI drugs, but any new drugs that come up
17 in that list, we would like FDA to have the list of
18 NTI drugs to be current and complete so there is no
19 last-minute surprise.
20 Also, if you look at the BE requirements
21 such as reference-scaled average BE and the two-
22 treatment, four-period, fully replicated crossover

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1 design, all these requirements for NTI drugs, if
2 they are not available early on, will help us to
3 develop products in a way that they meet all these
4 requirements.
5 So with this, I covered all four topics, and
6 I am giving back to Rob 10 more minutes so that he
7 can reuse for other purposes. Thanks, Rob.
8 Public Comment Period
9 DR. LIONBERGER: We'll definitely have more
10 discussion on that. But I appreciate identifying
11 that those topics are of interest to the industry
12 as well.
13 So now we'll move on to the open public
14 hearing part of the meeting. The first speaker is
15 Mansoor Kahn from Texas A&M University.
16 DR. KHAN: Howdy from Texas A&M and
17 greetings from NIPTE. So my two-cents words in
18 three minutes. All right? Hopefully, it will
19 address some of the research needs for the abuse-
20 deterrent formulations.
21 Obviously, we need some internal research in
22 FDA -- some of it, they've been doing

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1 already -- and some NIPTE and multi-institutional
2 studies, external research, internal and external
3 research.
4 This is a key slide for us. In the agency,
5 you have already looked at -- here is a list of 9
6 products, but 10 have been just approved now. So
7 on these product categories, one study category,
8 two, three, and four, they have been looked at.
9 You feel satisfied with these products, and you
10 have already approved those products.
11 Now, the internal research that is needed is
12 some of the reviewers or some of these folks or
13 scientists can go and look at how the postmarketing
14 changes are done because after the product is
15 approved, a sponsor looks at material changes, raw
16 material source changes, the analytical
17 characterization changes, SUPAC related stability
18 changes.
19 A lot of changes are made. And after those
20 changes, how is the sameness determined? You will
21 get very valuable clues from those things because I
22 think this morning she was saying about Ferrari,

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1 and Honda, and how do we go up to that destination.
2 So how did they go to their destination, the RLD,
3 to go to the sameness of the product? We can learn
4 a lot.
5 The second thing is, I think the agency has
6 been doing very good research here, understanding
7 all the variables, the product, and the process
8 variables for the data that is not submitted to the
9 agency without a response. So this is an example
10 of these three publications that are listed here.
11 So you are saying these publications here
12 vary our understanding of the formulation variable,
13 the process variable, the analytical
14 characterization that will help set the standard.
15 So I think this is the internal standard that
16 research is needed.
17 But honestly so, it has taken about five
18 years -- I was involved with this. It has taken
19 about five years to understand this one product of
20 OxyContin, and really we haven't spent a lot of
21 time because the product design and compositions
22 could be very complicated, coating methods, and

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1 goal is [indiscernible] combination.
2 So this work, if the agency tries to do it,
3 it might take them another 15 years. If you don't
4 want to wait for 15 years for the approval of other
5 generics, perhaps you can request -- I mean, you
6 can solicit external help here for critical
7 material attribute and critical process variables
8 of all products, all the 10 products.
9 So one is understood. The other nine
10 products, you can seek external help. The nasal
11 irritation studies, I think M.J. has asked for this
12 question, can be easily understood. And linking
13 the critical quality attributes with category 2, 3,
14 and 4. That's an important aspect there, but you
15 can seek external help.
16 I think NIPTE has been doing a consortium of
17 17 different schools. They've been working.
18 They've been doing a lot of work, and they really
19 have a lot of expertise. Purdue and Maryland has
20 already done some of the work for ADF. So NIPTE
21 can do the study. Thank you all very much, and I
22 will stop here. Thank you.

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1 (Applause.)
2 DR. LIONBERGER: Our next speaker is Dave
3 Schoneker, representing IPEC-Americas.
4 MR. SCHONEKER: Good afternoon, everyone.
5 IPEC-Americas appreciates the opportunity to
6 provide public comments at this meeting. Given the
7 increased understanding of the importance of
8 excipients to the quality and substitutability of
9 all generic drugs, we'd like to make the following
10 two requests, targeted at increasing FDA
11 collaboration and transparency with all drug
12 ingredient suppliers, not just API suppliers.
13 Much discussion occurred this morning about
14 API CQAs. As you've heard from previous speakers,
15 excipient CQAs are just as important and sometimes
16 more important.
17 So request number one is that IPEC-Americas
18 would like to recommend that FDA collaborate more
19 directly with members of the excipient industry to
20 ensure improved transparency in selecting the
21 specific studies to support and interpreting or
22 implementing results from the studies.

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1 The need for better understanding of
2 excipients, especially polymers and their role in
3 drug products, have triggered more technical
4 questions being asked of suppliers than in the
5 past. However, most excipients are produced by
6 chemical companies whose primary focus is not in
7 supplying to the pharmaceutical industry.
8 R&D resources in the chemical industry,
9 allocated to fundamental research, have been
10 significantly reduced in the last decade.
11 Therefore, if FDA is expecting a more fundamental
12 understanding of excipients and their CQAs, then
13 the FDA regulatory science initiative program will
14 need to help fund fundamental studies and research
15 in this area.
16 So IPEC-Americas is offering to collaborate
17 with FDA early in the process for any excipient
18 related projects. IPEC-Americas' subject matter
19 experts can contribute valuable knowledge and
20 experience to help FDA better select and design
21 projects to achieve their objectives. These
22 experts would also be instrumental in assisting

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1 with review and interpretation of results.
2 Request number two is that we've recently
3 met with the IQ Consortium and with members of FDA
4 for a critical path initiative or innovation
5 meeting. During the meeting, industry proposed a
6 critical path initiative for a novel excipient
7 qualification process, which was modeled after the
8 biomarker qualification process.
9 IPEC-Americas believes that there should be
10 a follow-up meeting with the FDA to discuss how the
11 CPI qualification process for novel excipients
12 being developed, which was discussed a little bit
13 more from a new chemical entity-type of novel
14 excipients so far, could be expanded to include
15 other types of novel excipients, which are used in
16 generic drugs such as co-processed excipients, new
17 grades of existing excipients within a family,
18 higher use levels than what is used in the IID,
19 and/or modified routes of delivery.
20 IPEC-Americas would like to collaborate with
21 the FDA to develop a qualification process, which
22 includes these other types of novel excipients used

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1 in generic drugs, thus minimizing and/or
2 eliminating uncertainties for ANDA applicants prior
3 to filing.
4 We're interested in meeting with FDA as soon
5 as possible to discuss the CPI process, how it
6 could be modified and used to support excipient
7 safety information in ANDAs. Thank you for the
8 opportunity to provide our comments this afternoon.
9 I will be filing detailed information to the
10 docket. Thank you.
11 DR. LIONBERGER: Our next speaker is Gordon
12 Amidon from the University of Michigan.
13 DR. AMIDON: Thank you, Rob. I want to give
14 a very brief three-minute update on the new science
15 of bioequivalence and what we're doing.
16 Of course, we want the patient to get a
17 product that works. Right? That's our goal, and
18 the pharmaceutical standards provide that. The
19 question is, what's going on in the
20 gastrointestinal tract when we actually administer
21 a product, since we've never done that? And those
22 are ongoing studies that we currently have. We

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1 intubate patients, measure four sites, stomach,
2 duodenum, jejunum, two places in the jejunum.
3 We measure the motility, shown on the right-
4 hand side, computer recorded, and a multi-lumen
5 tube. It's a complex tube. We have to do
6 overnight studies in humans. We can see the tube
7 placed into human subjects here, where we actually
8 simultaneously measure drug in the intestine and in
9 the blood simultaneously.
10 I'll just show that we measure the drug pH
11 buffer capacity, gastrointestinal concentrations of
12 drug, and plasma levels of drug simultaneously.
13 The most surprising and unusual results that we
14 have is, one, our test drug is ibuprofen, a low
15 solubility carboxylic acid. We call it a 2A for
16 low solubility acid.
17 It's in the intestine for seven hours. This
18 is an overnight study. We have the tubes in for
19 11 hours, but we can only do the study for seven
20 hours. Ibuprofen is in the intestine for 7 hours.
21 You can see it here in the blue. pH is in the red,
22 but the blue is the solution and the gray is the

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1 solid ibuprofen, in the intestine for 7 hours.
2 The reason for that is it's very low buffer
3 capacity. So it's not pH, it's buffer capacity
4 that's controlling the thing, and the buffer
5 capacity throughout the GI tract is on the order of
6 2. Our USP buffer capacity is around 20, that's
7 millimoles per milliliter per change in pH unit.
8 So we've got to pay attention to the buffer
9 capacity because that's why ibuprofen doesn't
10 dissolve in the gastrointestinal tract. When we do
11 the PK pharmacokinetic studies, deconvolution, we
12 see at 8 hours, about 80 percent of the drug
13 absorbed, so about 20 percent.
14 Seven hours is our last time point, 7 hours.
15 There's 20, 25 percent of ibuprofen that's still in
16 the intestine at 7 hours because of the low buffer
17 capacity. So those are the two that surprise me.
18 I think it surprises most people in our field
19 because we think of pH. We don't think of buffer
20 capacity. I learned it 50 years ago in physical
21 pharmacy when I took physical pharmacy, but I kind
22 of forgot about it after that.

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1 But at any rate, the next series of studies
2 is MRI studies of the human gastrointestinal tract,
3 where we actually measure fluid. We can also give
4 dosage forms at the same time, and we're cross-
5 validating the manometry method of motility, which
6 is the classical motility method, measuring the
7 pressure contractions in the intestine along with
8 the MRI studies, which are more generalizable. We
9 can do patients, we can do pediatrics, so I think
10 there's a bright future here for MRI studies.
11 Gastrointestinal variables to drug
12 absorption -- is it red? Okay. I'm done. My
13 slides will be available. Thank you.
14 DR. LIONBERGER: Our next speaker is Dr. Jim
15 Brasseur from the University of Colorado.
16 DR. BRASSEUR: Thanks. Gordon said only
17 three minutes before I came out.
18 All right. So I'd like to continue -- if I
19 could have the first slide. I'd like to continue
20 from Gordon's talk. So I'm part of the group at
21 the University of Michigan. I'm an engineer, but
22 I've been working in gastrointestinal physiology

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1 and mechanics for the past 30 years with regard to
2 drug absorption and release in the gastrointestinal
3 tract.
4 So one of the points that Gordon made that
5 they were carrying out these studies at the
6 University of Michigan in which they are measuring
7 in vivo quantities related to drug dissolution and
8 absorption. For example, here I'm plotting in the
9 right hand a single location in the intestine, the
10 variation in the pH.
11 You can see this is for ibuprofen. It
12 varies around the pKas, so as a result, solubility
13 varies dramatically with time as well. This is
14 also true along the gut, so if you measure other
15 variables such as concentration along the gut, for
16 example, and in the different gut segments, and
17 pockets, and so on, they vary dramatically, both in
18 the liquid form, on the left-hand side in the
19 jejunum and the duodenum, and on also the solid
20 form as well on the right-hand side. And as Gordon
21 has said, the solid form is lasting a lot longer
22 than had been previously appreciated.

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1 Why is that? Well, to a large extent, it's
2 because of the motility in the intestine, which is
3 extremely complex and has various components to it.
4 So in the middle picture, I'm showing Ehrlein movie
5 of the fed state in the dog. And you can see how
6 the changes in the volume of these pockets
7 dramatically is driven by the contractions of the
8 muscle wall, which is what's meant by motility.
9 Now, that moves content, including particles
10 and drug concentration, to the wall of the
11 intestine, where it can be absorbed. So if there's
12 a lot of variability in the motility, there's a lot
13 of variability in the absorption correspondingly.
14 It's more complex than that, however. At
15 the lower left, we are showing the fed state, and
16 in the middle, the fasting state. These are very
17 different and, in particular, for example, in the
18 fasting state, there's two kinds of peristalsis.
19 One is a global peristalsis, which follows the MMC3
20 contraction, and then there's local peristalsis
21 within the global peristalsis. And these are very
22 different speeds, and one can go antegrade, one can

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1 go retrograde, and so on.
2 The water pocket volume does vary
3 tremendously as well. Luca Marciari is part of
4 this group as Gordon mentioned, and he's measuring
5 huge variability in the volumes. So if you imagine
6 variability both in the content as well as in the
7 volume, you get huge variabilities in concentration
8 as well. So there's pretty much variability in
9 everything.
10 So when one is doing computer
11 simulations -- this is computer fluid dynamics,
12 computational fluid dynamics -- one has to take
13 into account these variabilities to predict both
14 the release and the absorption in the intestine.
15 And these variabilities will create different
16 levels of absorption with time and along the gut
17 and so on.
18 So I guess the take-home message from this
19 short discussion is that modeling frameworks, in my
20 view, in the future need to take into account the
21 stochastic nature of the drug release absorption
22 process. It should incorporate variability both in

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1 the model as well as in the predictions. Thank
2 you.
3 DR. LIONBERGER: Our final speaker is Robert
4 Page representing American Heart Association.
5 DR. PAGE: I want to thank the committee.
6 Again, my name is Robert Page, and I'm a professor
7 at the University of Colorado. And again, I'd like
8 to thank the committee to provide public comment on
9 behalf of the American Heart Association.
10 I'm going to take a little different stance,
11 so you're probably asking, oh, my gosh, what is he
12 talking about? But as an evidence-based patient
13 advocacy organization dedicated to improving
14 cardiovascular health for all Americans, the AHA
15 provides a unique role, and it has a unique role to
16 play in advocating both for the science
17 perspective, but also the health policy viewpoint
18 so that treatments are available, affordable, and
19 assessable.
20 As you've heard today many, many times, the
21 rising costs of prescription drugs is an important
22 concern, and in order to ensure that drugs are cost

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1 effective, we find that generics have been one of
2 those key sources.
3 The use of generic drugs has led to
4 substantial cost savings, and it has been brought
5 up that 88 percent of dispensed prescriptions are
6 generic and that only 28 percent of total drug
7 spending goes to generic drugs. However, I'm going
8 to advocate on behalf of the patient today here at
9 the FDA in the case of certain generic medications.
10 We have certain vulnerable populations,
11 heart transplant, post-myocardial infarction,
12 stroke, or heart failure in which a 30-day supply
13 of evidence-based pharmacotherapies are
14 unaffordable. For example, the out-of-pocket cost
15 for several evidence-based pharmacotherapies that
16 have been generic for several years is that of
17 digoxin, metoprolol succinate, and torsemide. The
18 cost of a drug that was \$1 is now about \$40. And
19 when you're on a Medicare part D plan, that's a lot
20 of money.
21 Colchicine, which is used to treat gout,
22 went from just a dollar to over \$150 for a 30-day

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1 supply. Why is this the case? We know. And
2 again, this committee has identified that already.
3 Smaller markets tend to attract fewer competitors.
4 Number two, mergers and acquisitions are occurring.
5 And for these reasons, consolidation is a concern
6 with regards to our patients.
7 The impact that we are seeing from a
8 clinical perspective within the community is the
9 fact that higher generic prices have adverse
10 effects upon everybody, from providers to patients.
11 Therapeutic advances in cardiovascular and stroke
12 treatment have greatly enhanced the lives of our
13 patients. And for that, I really truly want to
14 thank the Food and Drug Administration. But
15 affordable access to these medications,
16 specifically generic medications, is crucial if
17 you're going to prevent cardiovascular disease and
18 stroke. Therapies aren't effective if you can't
19 take them.
20 So with this in mind, as the FDA ponders
21 with regards to its research questions, I'm going
22 to pose a public health question. First of all,

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1 from a health services perspective, we should be
2 asking which of our vulnerable populations are
3 affected most by the rising price related to
4 generic prices?
5 Within these vulnerable populations, how has
6 rising generic prices impacted health outcomes from
7 both a health resource as well as a cost burden on
8 all stakeholders? And finally, the American Heart
9 Association is willing to collaborate with the Food
10 and Drug Administration in order to address these
11 issues.
12 I want to thank the committee for their
13 time.
14 (Applause.)
15 Panel Discussion
16 DR. LIONBERGER: Thank you very much. So
17 that concludes the open public hearing part of this
18 session, and now we'll move to the panel
19 discussion. So I'd like the panel to just briefly
20 introduce themselves and their affiliations,
21 starting on my right.
22 DR. BYRN: Stephen Byrn from NIPTE, and I'm

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1 a professor at Purdue.
2 DR. CONNOR: Dale Connor, director, Office
3 of Bioequivalence, OGD in CDER.
4 DR. GANG: Lucy Fang, team leader, Division
5 of Quantitative Measures and Modeling ORS OGD.
6 DR. HARAPANHALLI: Ravi Harapanhalli, senior
7 vice president, global regulatory affairs at Amneal
8 Pharmaceuticals.
9 DR. GOBBURU: Joga Gobburu, University of
10 Maryland.
11 DR. MEHTA: Yes. I'm Mehul Mehta. I'm a
12 division director in the Office of Clinical
13 Pharmacology, Clinical Pharmacology I, New Drugs.
14 DR. POLLI: My name is Jim Polli. I'm a
15 faculty member at the University of Maryland.
16 DR. SCHMIDT: Stephan Schmidt, associate
17 director for Center for Pharmacometrics and Systems
18 Pharmacology at the University of Florida.
19 DR. SEO: Paul Seo, division director,
20 biopharmaceutics, Office of New Drug Products,
21 Office of Pharmaceutical Quality.
22 DR. STIER: Ethan Stier, division director,

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1 Division of Bioequivalence II, Office of
2 Bioequivalence, Office of Generic Drugs.
3 DR. XU: Xiaoming Xu, senior staff fellow in
4 the Division of Product Quality Research in Office
5 of Testing, and research under OPQ.
6 DR. KIM: M.J. Kim, OGD, FDA.
7 DR. LIONBERGER: So to begin our discussion,
8 I'd like to begin with the topic of abuse
9 deterrence. So I've formulated the question here,
10 when we look, as M.J. mentioned, at what are
11 potential gaps and difficulties for the generic
12 industry in the development of abuse-deterrent
13 formulations, I think that the nasal abuse route is
14 the sort of area where there's the most challenges.
15 So I would like to initially open that up
16 for some discussion on the panel. So Xiaoming Xu?
17 DR. XU: First, I would like to say it's
18 really important from the agency perspective, from
19 the generics perspective, that we're looking into
20 the opioid drug abuse, and then the consequences of
21 the drug abuse leads to a lot of the sociological
22 and economical impacts.

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1 So from a research perspective, we know the
2 abuse, especially prescription drug opioid abuse,
3 is still involved in the field. Then this means
4 some of the methodologies that we may need to
5 utilize to study the formulation process quality
6 has to also be evolving over time. This is
7 normally applicable to the generic drugs and also
8 applied to the new drugs because, overall, this ADF
9 formulation is only a few years old. It's the
10 first product approved in 2010.
11 So there are a lot of needs in terms of
12 research. I guess in terms of the tools,
13 methodologies available, it's very limited for
14 nasal in particular.
15 I view there are a few things that could be
16 very important. The first thing, as we know even
17 for the locally acting how to study the nasal
18 sprays is still challenging, as discussed this
19 morning, but for the opioid formulation, especially
20 the formulation with a lot of polymers involved,
21 how do they get deposited at a different location
22 of the nasal cavity and what is the consequence of

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1 the absorption?
2 So a lot of the questions remain to be
3 answered. So that's my starting.
4 DR. LIONBERGER: Mansoor, are you able to
5 come to the microphone? I know you mentioned nasal
6 abuse in your talk, so if you can, I'm going to
7 follow up on your comments and your slides on that.
8 DR. KHAN: So I think you need to look at
9 the internal studies, just what did the RLD do for
10 the studies to get the label. And that will give
11 you very good clues for that one. Right? So just
12 the internal study is what I was pointing at.
13 DR. BYRN: I'm not sure I have an eye for
14 [inaudible – off mic].
15 DR. LIONBERGER: Yes. We're working on the
16 logistics.
17 DR. BYRN: Hey, I could just go away.
18 DR. LIONBERGER: Yes. Well, we'll actually
19 bring you the microphone. Steve, you can stay
20 there. You can just stay there. We'll bring
21 the --
22 DR. BYRN: I certainly agree with the nasal

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1 interest, but I think we want to maybe step back
2 and say what is causing the abuse-deterrent
3 epidemic or the problem and its deaths. And I
4 think it's mostly deaths by injection.
5 What's basically happening is people are
6 injecting medicine in their body, and they don't
7 know what the dose is. And obviously, these are
8 potent drugs, and they suppress respiration.
9 So what I would like to do is take off on
10 what Mansoor was talking about. I think we need to
11 focus on sameness determinations and also barrier
12 goals in the data submitted, especially related to
13 process and formulation because the drugs that
14 we're dealing with are extremely water soluble.
15 So we don't really have a problem with
16 anything. They're just very water soluble. So
17 what we need to know is how to formulate it and how
18 they're made. I think we need excipient
19 understanding from the speaker. I think the
20 excipients are playing a role, and we need to know
21 what that is.
22 The last thing, I was one of the

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1 investigators on the FY13 project, and it's out of
2 date now, four years old. I think there was only
3 one product when we started that investigation.
4 So we need to, again, continue to
5 investigate these products. It's a very
6 interesting area.
7 DR. LIONBERGER: Ravi?
8 DR. HARAPANHALLI: First of all, I think the
9 new guidance that came out last year, the draft,
10 which we believe will be finalized this year, it's
11 really a great step forward, and it draws from the
12 original guidance that was geared towards new
13 drugs.
14 Particularly, I like the idea of D versus R
15 versus C, the concept of a control as a way to
16 differentiate different tests and statistical
17 criteria.
18 Now, coming to this critical question, what
19 I feel is somewhat less focused in that guidance is
20 that it talks about the particle size ranges after
21 you grind material for certain defined amount of
22 period. And based on the sieving, you decide the

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1 study, and then you compare both RLD and the test
2 product. But it doesn't quite go into the fact
3 that the particle size itself could be different
4 for the API. It's possible that drug could come
5 out, and it could have its own unique particle size
6 distribution that's not represented by the cross-
7 measurement that we typically do, and that could
8 directly impact your in vivo nasal studies.
9 So if we can have a better in vitro
10 alternative where we can selectively measure the
11 API particle size in the ground material, maybe
12 MDRS or some other techniques, perhaps that would
13 serve as surrogates for doing such in vivo nasal
14 studies. So that's something that I think research
15 would be needed in that kind of area.
16 DR. LIONBERGER: One follow-up, one specific
17 area under the nasal abuse that's of potential
18 research interest is in the role not just of the
19 physical barriers, but of the aversive nature of
20 the components.
21 So any comments on how to evaluate that and
22 I think whether other components in the formulation

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1 may have an impact on the drug aversion?
2 DR. XU: For the aversive effect, we're
3 trying to look at it as a purely technical
4 consequence of the material triggering some
5 reaction. But in a lot of ADF formulations, use of
6 the polymers, especially high-molecular polymers
7 can also introduce physical discomfort, which in a
8 way also is introducing the aversive effect even
9 though not specifically aversive agent.
10 But I guess the challenge is how do you
11 quantify the irritation or potential of molecules
12 of materials without doing in vivo study? And is
13 there any way to come up with in vitro studies or
14 even somewhere in between, intermediate, to look at
15 the irritation potential because this is related to
16 physiological response of the physiology as well as
17 the psychology of the sniffing the material into
18 the nasal cavity.
19 DR. HARAPANHALLI: By definition, the
20 aversive agent is meant really to inflict certain
21 discomfort when somebody tries to abuse it. So
22 that said, I don't know if there can be any

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1 alternative in vitro or animal models that can
2 reliably predict that. It is something very unique
3 to humans that they either like it or dislike a
4 particular formulation when they try to abuse it.
5 So I'm not very sure that there can be any
6 better alternatives other than actually doing a
7 usability-type study.
8 DR. LIONBERGER: Just a question, as you
9 look ahead, are there any other areas -- I mean, we
10 focus here on what are in the currently approved
11 reference products? That's the starting one. Are
12 there any sort of research frontiers that we should
13 be looking ahead to prepare for the next
14 generation -- I think the question was get the
15 science done ahead of time.
16 So let's do some horizon scanning and say,
17 what are the emerging areas in abuse-deterrent
18 formulations that you think need to be prepared for
19 the next generation of generic products?
20 DR. BYRN: Of course, being a professor, I
21 think we need to look at things in the future. But
22 let me suggest that there might be a way to do

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1 this, which would be to look at patent
2 applications, because I'm guessing that people are
3 putting in things pretty quickly after they
4 discover an approach.
5 So there may be a strategy to review those
6 documents and then to make a determination of which
7 of the approaches appear to be most likely to move
8 forward and to carry out a study following that.
9 DR. XU: As we understand, in vivo studies
10 are quite difficult to conduct, especially related
11 to ADF studies because if you are aware of the
12 labeling guidance for the ADF product, there is
13 category 1, 2, 3, 4 studies.
14 But as you move up the categories, they're
15 difficult to increase because it's involving human
16 subjects, which means how to evaluate the
17 effectiveness of the abuse deterrence potential in
18 a human liability -- drug abuse likeability study.
19 So certainly, if there are in vitro tools
20 available, it will help to shorten the time or save
21 the cost of conducting the in vivo studies. And
22 also, we know the AD properties is part of the

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1 product qualities due to the formulation design,
2 due to the manufacturing processes.
3 It's suspected to be intense throughout the
4 product shelf life and during the stability, so how
5 do we determine the AD property and AD potential of
6 postmarketing? So certainly, if there is in vitro
7 tools, in vitro methodologies available, and
8 preferably standardized in vitro methodologies
9 available, that will help to ensure that the AD
10 properties can be maintained even postmarketing.
11 To extend on that, also the category 2 and
12 category 3 studies rely on the category 1 study,
13 which is in vitro. So how do we find vast in vitro
14 markers or the surrogate properties in order to be
15 more representative and then to give better
16 information to guide the category 2 and category 3
17 studies? That will be I think the very important
18 to look in and to do more research.
19 DR. LIONBERGER: One final discussion point
20 of this is, we've got some expertise in PK/PD
21 modeling here. Can we talk about what are some of
22 the things we should be looking for as we try to

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1 understand the PK/PD relationships for
2 abuse-deterrent formulations. Sometimes all of
3 these products get labeled claims by a drug liking
4 study, which is really a pharmacodynamic endpoint
5 that's the basis for approval.
6 So comments on how our understanding about
7 the pharmacodynamic effects of this drug may help
8 pathways for generic products, so I would
9 appreciate any comments on that, just any member of
10 the panel.
11 DR. SCHMIDT: So maybe it would be important
12 to look at this not necessarily from a
13 switchability point of view, but from an exposure
14 response point of view, saying which processes play
15 a role. So we have of course in the practice
16 setting also the potential of drug-drug
17 interactions of uptake or drug-drug interactions in
18 the field with uptake across the blood-brain
19 barrier.
20 For example, for oxycodone, you have 2D6
21 also in the brain. And if you have a combination
22 in the practice setting that would inhibit, for

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1 example, PgP in the blood-brain barrier, plus you
2 have flagged a subpopulation that would be a poor
3 metabolizer or other metabolizers for 2D6, that may
4 play an important role.
5 Again, this is not necessarily a
6 switchability question, but I think, particularly
7 for colleagues at FDA, this would also provide an
8 opportunity to learn from -- that would provide an
9 opportunity to learn from the colleagues at the
10 Office of Clinical Pharmacology, for example,
11 because, I mean, they look into this type of
12 question for new drug applications anyways.
13 DR. GOBBURU: I see the role of
14 generalizability. We can use quantitative
15 approaches for that in two dimensions. One is
16 going to be in terms of understanding the
17 relationship between the level of abuse deterrence
18 and its impact on the potential development of
19 dependence and such.
20 Understanding that relationship will give us
21 one dimension of specs in terms of what type of
22 abuse-deterrent characteristics would lead to

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1 clinically meaningful differences, especially on
2 the lower side, not so much on the higher side.
3 The other dimension would be to understand
4 the contribution of the different excipients that
5 are used for making the product abuse deterrent and
6 how that's impacting the product performance. So
7 it's the excipients to the product to some kind of
8 a patient sign or symptom with respect to abuse.
9 If we can understand that -- and in fact,
10 that's the only way I see, actually, that we can
11 solve this problem of substituting in vivo studies
12 with the in vitro or in silico studies. If you
13 think about it, maybe it's a different take by the
14 agency, but the stakes of making a mistake is
15 pretty high, and people are nervous about it, both
16 public as well as the government.
17 So until we have adequate experience, but
18 with a commitment to develop such an understanding,
19 asking more studies, I don't see that as
20 unreasonable.
21 DR. POLLI: I would just totally agree with
22 that. So I'm going to make comments even though

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1 I'm just not an expert in this area. And what I
2 was thinking about was Dr. Amidon's slide, which
3 was very new to me, about ibuprofen is very
4 familiar, and we like to think we know a lot about
5 maybe the absorption of that drug, but maybe we
6 don't know so much.
7 So I would agree that, given this issue,
8 yes. Maybe in vivo studies are difficult to do,
9 but isn't this topic worth it? And quite often, in
10 formulation, we probably don't do enough in vivo
11 investigations to understand the importance of
12 formulations. So yes, maybe in vivo studies really
13 need to be done.
14 I guess the other thing I would say about
15 in vitro is if we can dial back to the mid-90s, it
16 would have been a good thing at that time to
17 implement in vitro tests, even though maybe not
18 everything was known. And I think a lot of people
19 would probably say yes to that.
20 So sitting here today, yeah, there's a
21 strong reason to develop in vitro alternatives,
22 even in the absence of perfect information.

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1 DR. LIONBERGER: I think with that comment,
2 we'll move on to our next topic, talking about the
3 BCS class 3 waiver question. So I think we heard
4 in the industry presentation concern that one
5 reason why the generic industry doesn't use the BCS
6 class 3 waiver option is the formulation
7 differences.
8 I want to confirm with our industry
9 colleagues that you think that's an accurate
10 representation of the decision-making processes you
11 go through when you consider whether to use a BCS
12 waiver or not.
13 DR. SEO: I don't know about the generics
14 scene with regards to Q1/Q2, but even on the new
15 drug side, we have turned down requests for BCS
16 class 3 because, primarily, one, the guidance is
17 still in draft and, two, we're still building our
18 knowledge base.
19 I think it's probably relative. We're being
20 conservative until we know more. And then we can
21 perhaps visit the idea of expanding beyond Q1/Q2.
22 But for now, I mean, guidance just came out, so I

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1 think we're still building our knowledge base
2 there.
3 DR. AMIDON: I think probably the
4 requirement for quantitative similarity,
5 quantitative sameness is maybe too strict. But you
6 need to do that the first time to get your feet on
7 the ground. But then I think excipients
8 desperately need a classification system.
9 I think IPEC made some proposals there. I
10 think certain excipients are safe. Of course it's
11 a dose-response curve. It's pharmacology, so I
12 think it desperately needs a classification system
13 for excipients.
14 DR. LIONBERGER: Yes. In terms of timing,
15 right, now that the guidance is out for the Q1/Q2,
16 that's sort of a settled issue. So the research
17 frontier is what do we do next. So I think that's
18 what is on the research agenda.
19 I want to Mehul can you give a little
20 background on what the concerns were about
21 differences in formulation for class 3?
22 DR. MEHTA: Yes. So actually, it's one of

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1 the bullet points in M.J.'s slide. When we started
2 devising our 2000 guidance in the BCS committee,
3 this was around 2012, 2014. I think it was before
4 even GDUFA was approved.
5 So at that time, when we looked at it
6 internally, we did see examples, especially for
7 very low permeable drugs like bisphosphonates.
8 There was impact of excipients on bioequivalence
9 outcomes for those products.
10 Then we have seen very few examples in
11 literature, but academicians do pose those issues
12 that excipients affect transporters. My personal
13 take is, it is surfactant type excipients that
14 largely do it, but that's sort of an unsettled
15 issue.
16 The third thing, then, we looked at was
17 other agencies' position on this. The EMA was out
18 there in 2010 with their finalized view on this,
19 and they are maybe even more conservative than us.
20 So in the absence of objective data, Siva
21 mentioned something, and I would like to ask him a
22 bit more about it. But in the absence of objective

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1 data, if for example, in reality the excipients
2 using IR and MR products have no impact on the
3 permeability of APIs with the exception of
4 [indiscernible].
5 So it would be wonderful if that was in the
6 public domain, if it was analyzed and published.
7 We would love to use that. But short of objective
8 data, which we didn't have at that time, we had to
9 start with that position. Since then, Jim has been
10 working on the project for us, which was finally
11 concluded and nice results there. So it does
12 identify maybe like 10 excipients that don't affect
13 total prototype class 3 products. But again, that
14 is still being debated in the literature somewhat.
15 That was the real reason we started the
16 position. I think, personally, there is room for
17 growth very rapidly. Ethan is working on something
18 internally right now, and I don't know if we'll
19 have time to talk about it.
20 But lastly, we are dealing with the same
21 issue with ICH also. This is one of the important
22 issues that we want to resolve. And I think PhRMA

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1 is working very vigorously on this issue, I think,
2 along with IPEC folks.
3 So we have hopes of identifying excipients
4 maybe on the lines of what Gordon was hanging up,
5 classes of excipients where it'd be nice to have a
6 no-problem excipient list where we know enough
7 about them.
8 So that's a long answer, but the reason why
9 we started that position -- and in my opinion,
10 there is hope for very rapid improvement there.
11 Internal work is going on, and I think at ICH, a
12 lot of us are working on this same issue, and of
13 course in personal academia, it is very useful.
14 DR. LIONBERGER: Jim?
15 DR. POLL: Yes. Mehul mentioned a study
16 that we did, actually a series of studies that we
17 did, resulting in a publication maybe one or two
18 years ago involving 14 common excipients. This was
19 FDA funded, so it was very collaborative in terms
20 of the design of the experiments, selection of the
21 excipients, these common excipients.
22 The result was, for 12 of them, there was

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1 bioequivalence. And I would say an absolute
2 massive amount of excipient was used in each of
3 those 12. There were an additional 2 where Cmax
4 did not quite hit, so maybe couldn't rule out an
5 excipient effect.

6 So for at least those 12 very, very common
7 excipients, we concluded that they need not be Q1
8 or Q2. This was in the Journal of Pharmaceutical
9 Science as I recall, and interestingly, there was a
10 letter to the editor by some folks saying, we
11 disagree that it should be generalized. It's okay
12 for those two drugs that you studied, but all of
13 the other drugs, maybe not. I think that's a valid
14 point of view. It's not one I happen to agree
15 with.

16 So that's maybe one issue, just how
17 generalizable it is. And obviously, you can
18 imagine combinations of excipients and things of
19 that sort.

20 One thing worth mentioning that I think Rob
21 already mentioned was just the active transport.
22 You probably would worry about a compound that's a

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1 substrate for some sort of active transport process
2 and an excipient modulating that. But there's
3 probably ways to actually answer that. That could
4 be done.

5 DR. LIONBERGER: Charlie?

6 MR. DiLIBERTI: You need to take into
7 account the practical issues for the generic drug
8 manufacturer. They don't have the benefit of the
9 innovator formulation. They have to determine how
10 much excipient is in there by analysis. And if the
11 innovator puts a milligram of a particular
12 excipient into a formulation, but they have process
13 loss of that excipient, there may only be
14 0.9 milligrams in the formulation. Automatically,
15 then, you're outside of Q1/Q2, which has to be plus
16 or minus 5 percent.

17 Also, Office of Generic Drugs does not
18 confirm. When you submit a letter on one of these
19 BCS class 3 waivers, you submit a letter, here's
20 our proposed formulation, is it Q1/Q2, no answer.
21 So it really puts generics in a bind.

22 DR. LIONBERGER: I think the question on the

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1 control correspondence, I think we need to think
2 about ways that that can be answered and how to
3 answer those questions. And I think that's
4 something definitely to take back to think about
5 the process around this, where we have guidance
6 that asks people to be very similar, but have a
7 mechanism for which they can actually get some
8 feedback on that answer for that specific product
9 category.

10 MR. SCHONEKER: I just want to follow up a
11 little bit on Dr. Mehta's point. We are at IPEC
12 aware of the ICH discussions that are going on.
13 And we have put together a group of experts,
14 formulators, et cetera that are currently putting
15 together a list to try to, at least as a first
16 pass, give some ideas about which excipients and
17 which modes of action might be more risky,
18 et cetera, and less risky.

19 I think to your point, Jim, our opinion is
20 it really depends on not the excipient, but what
21 the function of the excipient is in a particular
22 formulation and what the other formulation

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1 ingredients are.

2 Now, that said, there may be some
3 generalities that can be taken as far as where
4 there's more risk or certain excipients that might
5 fall into different modes of action. So we're
6 trying to come up with a list that might be helpful
7 to the ICH group and FDA ultimately as to what are
8 some excipients to take a look at from different
9 perspectives and where there might be less risk and
10 more risk. And then that might also give some
11 ideas as to where some additional research might be
12 done, what type of studies to justify some of those
13 interpretations from experts, if you will.

14 DR. SCHMIDT: Not to play devil's advocate,
15 but maybe since FDA is also looking for some ideas
16 for future research, as far as I'm aware, the
17 ICH-E7 guideline also recommends the inclusion of
18 special patient populations, up to 10 percent of
19 elderly populations, for example.

20 So the question would be, do the results
21 from a bioequivalence in health volunteers
22 translate 1 to 1 in special patient populations

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1 such as the elderly or in children, given their
2 potential difference in pathophysiology such as
3 altered pH or gastric motility, and to what extent
4 does this change the benefit-risk profile for
5 excipients. So for example, HPMC, given that it's
6 a pH-dependent solubility profile.
7 DR. LIONBERGER: Aloka?
8 DR. SRINIVASAN: I'd like to just bring up
9 an interesting issue. I think, Mehul, I had talked
10 to you about this some time back. When you are
11 talking of Q1/Q2, I do remember when in FDA we had
12 an issue with locally-acting tablets which worked
13 locally. The innovator went and said just starch
14 in the label, however, we internally knew what kind
15 of starch was being used. When somebody uses corn
16 starch versus pregelatinized starch, everything
17 changes.
18 So here, I can understand where I was. I
19 could not tell them, guys, do not use
20 pregelatinized, use cornstarch. So now we are
21 going into this -- like there are many vegetables,
22 choose one of them, et cetera, et cetera.

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1 I think this is something FDA might face
2 when you talk about Q1/Q2, and you will need to
3 understand, like, can change -- just an example,
4 pregelatinized versus cornstarch, would it make a
5 difference? I think it would, but every product
6 there will be a struggle there. So that's
7 something we need to keep in mind about this.
8 About the abuse deterrence, changing topic
9 there, it's something that always haunts me. What
10 if an innovator is abuse deterrent by the pathway
11 AB, but a generic can make a product, which has an
12 additional abuse deterrence? How is OGD going to
13 deal with that?
14 That's something we need to understand. If
15 they want, will there be a label change, and how
16 will the science support it and everything. I just
17 wanted to bring this up, just food for thought,
18 probably.
19 DR. LIONBERGER: Let's move on to our next
20 topic. So I formulated the question here, talking
21 about using integrating predictive dissolution
22 methods, PBPK and PK/PD modeling for decision about

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1 generic drug bioequivalence standards.
2 So I think we heard from the industry
3 perspective that the point that's most painful to
4 the generic industry is when we make these
5 decisions later, so it impinges in the development
6 or even the review timeline.
7 So I'd like to ask the panel, are there ways
8 that we can use these tools to make decisions
9 specifically about partial AUC, different
10 bioequivalence standards, or different
11 bioequivalence expectations for various things that
12 appear in the label or are needed to ensure
13 therapeutic equivalence earlier.
14 So just broadly as that topic first to say,
15 looking for that early decision point.
16 DR. MEHTA: Obviously, this is a topic of
17 great interest for me on the new drug side and
18 Ethan and others and Dale on the generic drug side.
19 But we need to start thinking about these issues at
20 the time of approval of new drugs. If there are
21 going to be specific issues to worry about in terms
22 of bioequivalence issues of this innovator products

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1 post-approval, they should be held to the same
2 standard as OGD ANDA drugs.
3 So the knowledge base that needs to
4 developed for identifying these issues and how to
5 resolve them needs to be put together at the NDA
6 stage. And then as now, we are working more
7 collaboratively between new drugs, generic drugs
8 through an NTI working group or other mechanisms.
9 That's the best way of, sharing information
10 to the OGD colleagues, what's being done at the new
11 drug stage. Then we can pass down that knowledge
12 in time for OGD to prepare their product-specific
13 guidances that are most informed.
14 DR. SEO: To add to that, we've had
15 instances where we've done PBPK modeling
16 essentially in the new drug space. The difficulty
17 is when we try to apply the framework of that model
18 to a generic drug, the legality of how much of that
19 model can be shared, because not all of the
20 information can transpose between applications.
21 So after we strip away from our NDA model
22 the things that are proprietary, essentially,

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1 there's not much usable model left. In some
2 instances, there are when the model is built on
3 completely public information, available
4 information. But for us, that has been the
5 difficulty in implementing PBPK at the application
6 stage for generic.
7 The other part of that is when we've
8 requested that information in the ANDA, we often
9 get a lot of pushback, and obviously so, because
10 during the time of application, it's kind of late
11 in the game to all of a sudden try to model
12 something, especially if you know the agency is
13 doing that.
14 The difficulty on the GDUFA and ANDA side
15 also is currently we don't have, except for the
16 PSRs, a paradigm to initiate those conversations
17 with you guys early in terms of you should try
18 this, modeling a simulation, this is how you should
19 go about doing it, these are the kinds of things we
20 expect, where in GDUFA, we have so many avenues to
21 have those discussions early.
22 So that's been a real challenge for us, and

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1 we've been messaging it forever in terms of try
2 this out, try PBPK, try modeling the simulation,
3 especially in the quality realm. But it is a
4 challenge, but I reiterate that message here, I
5 guess.
6 DR. AMIDON: Paul, yes. We all appreciate
7 the public policy issues you have to deal with
8 because that's public policy. But I'll go back to
9 what Mehul was saying. I think you're touching on
10 what I think is maybe the biggest soft spot in our
11 industry because the commercial innovator product
12 has to be bioequivalent to the phase 3 product.
13 Right? Because the phase 3 product is the only one
14 we have data for. Everything on the market has to
15 be generic, including the innovator, to the phase 3
16 tested product.
17 The dissolution standard on the phase 3
18 product should be our pivotal standard if we had a
19 good dissolution test.
20 DR. MEHTA: Just to clarify what I was
21 saying, my comments were mostly restricted to if we
22 need to worry about additional BE criteria for a

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1 specific product like partial AUCs, things of that
2 nature. And that's what we have done for, for
3 example, methylphenidate products, Ambien CR.
4 We had a lot of good data at the NDA stage
5 for us to evaluate those issues properly. So we
6 had to worry about that at the NDA stage. And then
7 we brought it over, and our OGD colleagues worked
8 further on those approaches.
9 When we worked on it, of course, all very
10 extensive and sophisticated modeling approaches
11 were used, and Joga was one of the main architects
12 of that. So there is definitely a lot of scope and
13 potential for it. We just need to continue to work
14 better on it and more collaboratively.
15 DR. LIONBERGER: Joga?
16 DR. STIER: Sorry, Joga. Yes, Joga was
17 heavily involved in that. I agree with most of the
18 comments said already that for the methylphenidate
19 products and the Ambien, which I believe there was
20 an advisory committee at the time a few years back,
21 that was really an evolution.
22 Part of that was a combination of, one, I

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1 think having a long history of understanding that
2 there were strong PK/PD relationships for the API,
3 but I think the new layer that got added on is
4 there's kind of a delayed or lag time, if you will,
5 between new formulation technology that's
6 potentially used on the innovator side, and then
7 those products, when they come off patents,
8 generics are trying to match those characteristics.
9 I think some of the approved labeling for
10 some of the products that we're talking about,
11 where that's actually incorporated in the language
12 of labeling, that the product is designed in a
13 particular way to deliver drug for which there is a
14 strong PK/PD link. And the way in which it's
15 delivered is very important to the therapeutic
16 efficacy of that product.
17 So that led to this evolution in thinking on
18 these types of products, in a timely way I think.
19 And I think that, although it hasn't been I guess
20 ratified, if that's the right word, but at least in
21 the drafts of the GDUFA 2 commitment letter, I
22 think that in a sense will be driving a lot of

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1 discussions earlier on.
2 I mean, the point's well taken that that
3 information can be more given out in a timely way
4 to industry so they can potentially conduct those
5 appropriate studies or take that into account into
6 their design or their formulation to match those
7 critical characteristics, I guess, of the brand
8 name product.
9 DR. LIONBERGER: Joga?
10 DR. GOBBURU: This topic is too broad, so
11 I'm going to make three comments. If there is a
12 specific question we want, we can talk about it.
13 The first thing is, I would strongly advise
14 you all to reconsider the wording. I know this is
15 for a discussion, but the wording, my advice is to
16 keep it disciplined with respect to the ultimate
17 decision, not so much about the methodology. So I
18 would probably say something like efficacy-,
19 safety-driven bioequivalent standards.
20 You can say by integrating dissolution PK
21 exposure -- I mean PK efficacy and safety, I would
22 leave the PBPK part, PK/PD modeling, sometimes you

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1 don't need some parts of that. So it makes it a
2 little bit flexible for people who use innovative
3 methods, but reach the same conclusion. That's my
4 first reaction.
5 The second one is, in my opinion, the
6 modeling that is done, any of this modeling that is
7 done to support a NDA or a BLA are going to be very
8 different from the models that you would need for
9 driving these bioequivalent standards.
10 The resolution that you need the signal to
11 noise, the resolution you need for the NDA BLA is
12 pretty low, meaning you are trained to come up with
13 big effects. But for generics, you want to be able
14 to detect reasonably small changes, so the modeling
15 has to be very different for this purpose than that
16 goes for the approval and labeling decisions.
17 The endpoints will be different. You can't
18 do a survival endpoint for bioequivalence
19 standards. You will have to go to the biomarker,
20 which is reasonable and also more sensitive to the
21 changes in the PK. So these models will be very
22 different from those you will need for approval and

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1 labeling.
2 The third point I have is, I do not see how
3 the innovator would have any skin in the game on
4 this one. If I were the innovator, I would
5 probably do bioequivalent studies for my own
6 compatibility issues and changes rather than invest
7 in this kind of stuff and save the world.
8 So I think FDA is the only organization
9 which can do this. Perhaps there has to be a joint
10 division between OGD and OCP or something like that
11 to cater to this.
12 DR. LIONBERGER: Dale, then Lucy?
13 DR. CONNER: We've talked a lot about
14 modeling today, and modeling for approval purposes,
15 modeling for policy development, or modeling for
16 just learning. Unfortunately, if you're not a
17 modeler or have not dealt with it very much, you
18 sometimes naively think, oh, well, I'm just going
19 to do a model instead of doing real data, and that
20 doesn't usually work.
21 As most modelers will tell you, you need a
22 basic understanding or at least a starting point to

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1 be able to construct your model and have it mean
2 anything. Granted, models sometimes lead you down
3 wrong paths, which you learn from, and they are
4 very instructive about getting to the point of
5 understanding. But the best modeling is done in an
6 iterative process. You take basic data, you
7 develop a model, and you test it against some more
8 real data. And you kind of iterate back and forth
9 until you get something that meets your needs,
10 which is never perfect in ever the entire universe.
11 So a lot of these models, it's not really
12 either do studies, real studies, or do modeling.
13 It's really, you should do both. And they should
14 interact effectively to increase knowledge. And
15 we're talking about modeling here or methods to set
16 bioequivalence standards.
17 I mean, I can't just do what I do now, and
18 model it, and just hope for the best that I'm going
19 to make the right assumptions, and put the right
20 structural model together, and so forth, and come
21 up with the answer. I really have to mix that as a
22 tool for understanding with real data.

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1 So it doesn't really get us out of the
2 expensive, onerous doing real human or other types
3 of data. It just enhances that and enhances our
4 understanding.
5 I also think that a lot of the knowledge
6 that we would put into a model or put into
7 understanding, for example, our knowledge of
8 excipients, really, I'm almost amazed that every so
9 often, we find out something really brand new to
10 us, anyway, about some excipient that we've used
11 for 30 or 40 years.
12 The example that comes to mind is sorbitol
13 or other alcohol sugars. We often assumed that in
14 the regs, which were written a long time ago, if
15 you have a solution, a solution dosage form,
16 everything is in solution, excipients, the active.
17 What could go wrong? We should just waive that.
18 And then we discovered much later in the game that
19 alcohol sugars for certain types of products really
20 affect them, even though they're in solution
21 already.
22 That was a very BCS type of finding. We

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1 didn't understand it way back when those regs were
2 written, but now with the BCS data and the
3 understanding that that brings us, we now kind of
4 understand what's going on with that.
5 But there are probably other things lurking
6 out there where we assume we know quite a lot and
7 we don't really know as much as we think.
8 Modeling, and real studies, and real
9 biopharmaceutical studies will help us understand
10 that, but I don't think we're still at that perfect
11 level of knowledge about even inactive ingredients,
12 and not only the inactive ingredients in isolation,
13 but how they interact both with each other and the
14 drug substance because something could be good for
15 the first 100 products you use it in. But you use
16 that 101 product with another excipient, and they
17 both interact in some way with the drug, and all of
18 a sudden, all that I thought I knew is not quite as
19 accurate as I thought it was.
20 So I think we should use modeling as a tool,
21 but understand that it's not like the magic bullet
22 that's going to solve all our problems.

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1 DR. LIONBERGER: Lucy, and then Raj?
2 DR. FANG: We heard from our industry
3 colleagues today that we really want FDA to share
4 alternative BE recommendations and the prospect
5 proactively and also in a timely manner. So how
6 can we get there?
7 So we heard from Mehul, we can enhance
8 OGD/OND collaboration. We gain better
9 understanding from the new drug development. The
10 other way is that we can feel the gaps in our
11 knowledge base, and that's where we are with the
12 regulatory science program.
13 So Joga, you mentioned that the models for
14 the new drug and generic drugs could be very
15 different, so I would like to hear more thoughts
16 from you, other research needs in this regard.
17 DR. GOBBURU: If you think about this
18 problem from the clinical end all the way to the
19 product, the excipients and such, that's how I
20 would think it would be most meaningful. First, we
21 need to find an endpoint. It doesn't need to -- it
22 probably cannot be in most cases. It doesn't need

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1 to be an endpoint based on which the drug is
2 approved. It should be an endpoint that means
3 something to the efficacy or the pharmacological
4 activity more so, not just efficacy, but
5 pharmacological activity.
6 So you need to find one or two, preferably
7 one, biomarker endpoint which is sensitive enough
8 to the changes in concentrations. You don't want
9 to have an endpoint which is cumulative, like
10 survival, which probably doesn't move even if you
11 half the dose or double the dose probably.
12 DR. FANG: So you want more from an endpoint
13 perspective.
14 DR. GOBBURU: No. That's one big change
15 from the NDA BLA views, because that's all focused
16 on approval endpoints, mostly.
17 DR. FANG: So the question I would like to
18 ask is from a broader perspective, from a technique
19 perspective.
20 DR. GOBBURU: I see. We talk about this,
21 and there are technologies and expertise to do each
22 one of them separately, but I have never seen

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1 anybody put them together.
2 DR. FANG: Maybe we can table this for our
3 next session. We have a next session.
4 DR. LIONBERGER: So we've reached the end of
5 our time. The alarm's going to go off in five
6 seconds. I'm not immune to it. And so we'll be
7 back in 10 minutes at 2:45 for our modeling and
8 simulation final session, so a 10-minute break.
9 (Whereupon, at 2:35 p.m., a recess was
10 taken.)
11 DR. CHOI: We will go ahead and get started
12 with our last session. Our last session will be on
13 computational and analytical tools. And I would
14 like to introduce our first speaker, Dr. Liang
15 Zhao. He is the director of the Division of
16 Quantitative Methods and Modeling at FDA, and he
17 will be giving us an FDA research update.
18 Presentation – Liang Zhao
19 DR. ZHAO: Good afternoon, everyone. This
20 is the last session of the full day. So from
21 previous presenters, especially from FDA presenter
22 Dr. Markham Luke, M.J. Kim, you can feel a thread

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1 of a modeling simulation component in the thinking
2 in the current generic drug review development.
3 I'm here to download you more with some
4 thinkings within and also want to sincerely seek
5 your input regarding using modeling simulation to
6 support the GDUFA regulatory science research
7 program.
8 So after an introduction on generic review
9 and development, I will give some impacts made by
10 quantitative methods and modeling on
11 physiologically based PK model, pharmacometrics,
12 quantitative clinical pharmacology, and big data
13 analysis. At the end, I will critically go over
14 some relevant GDUFA-funded research contracts, and
15 most importantly welcome your critical input in
16 some of the regulatory research areas.
17 There are similarities and dissimilarities
18 between new drug and generic drug application
19 package. From the previous panel session, we have
20 been hearing about the modeling simulation, the
21 purpose, and the utilities are different for new
22 drugs, and generics and I fully agree on that.

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1 However, what is common for both new drugs
2 and generic drugs that will include components for
3 drug substance, manufacturing, drug product,
4 natural biology, biopharmaceutics in the
5 application package.
6 In contrast, the bioequivalence study in the
7 ANDA package is a counterpart of pre-clinical
8 studies, clin pharm, and clinical studies that are
9 included in the NDA package.
10 One key underlying question that can be
11 addressed by a bioequivalence study is whether the
12 drug is delivered to the action site in the same
13 way for different formulations. If the answer is
14 yes, brand products can be substituted by generics
15 upon their approval.
16 The division of quantitative methods and
17 modeling in the Office of Research and Standards
18 holds several key tool sets to address existing and
19 forthcoming challenges. They include the release
20 and absorption PBPK models for oral and non-oral
21 routes of administration and the pharmacometrics
22 approach consisting of population-based PK/PD

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1 modeling on exposure-response models. The third
2 component is the big data tool, including analytics
3 for complex mixtures, systems pharmacology, risk
4 models, and business process models. I'll give
5 some examples in the following slide.
6 We are also actively pursuing other novel
7 methods to support generic drugs, guidance
8 development, and regulatory decision-making.
9 Modeling and simulation has made a critical
10 impacts on various regulatory activities in the
11 Office of Generic Drugs. This slide gives a high
12 level of summary modeling and simulation products
13 that has made a contribution in the Office of
14 Generic Products within calendar year 2016. They
15 correspond to early and late stages of drug
16 development, including guidance development,
17 especially product-specific guidance, to lay out a
18 regulatory pathway forward for the generic firms ,
19 pre-ANDA interactions, including pre-ANDA meetings,
20 and controlled correspondence, and consults during
21 ANDA reviews and citizen petitions mostly before
22 new drug or ANDA approval. Certainly, all of this

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1 is supported by a broad array of regulatory
2 research studies. Quantitative methods and
3 modeling are closely related to all these
4 activities.

5 As discussed from an earlier session, in
6 comparison to new drug applications, most of this
7 modeling effort was initiated within the agency
8 under the support of GDUFA regulatory science
9 research program, reflecting the importance of
10 regulatory science innovation in the generic drug
11 program.

12 Overall, the OGD, Office of Generic Drugs,
13 uses modeling and simulation to evaluate deviations
14 from guidance or unusual review situations. The
15 generic industry could use model-informed drug
16 development. We call it MIDD. It's named from the
17 PDUFA negotiation before they proposed novel method
18 in an ANDA to support new BE approaches. The
19 reason is to accelerate development and review of
20 complex locally-acting product by such
21 methodologies.

22 Given its importance, I want to allocate

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1 several minutes to talk about the physiologically-
2 based PK modeling in the realm of generic drug
3 development and attention received from both new
4 and generic drug industry. FDA and academia have
5 reflected the establishment of general guidances,
6 AC meetings, and the mainstream scientific
7 conferences.

8 Based on the route of drug administration,
9 PBPK models can be divided into oral and non-oral
10 absorption models. Oral absorption models are
11 established and are commercially available and are
12 useful to FDA and the industry. Non-oral
13 absorption models are at a relatively earlier stage
14 of development, but are critical to FDA and the
15 generic industry, especially for establishing
16 abbreviated pathway to evaluate locally-acting
17 drugs.

18 Physiologically-based models generally
19 involve two sets of parameters. One set is drug
20 product specific and the other set is drug and
21 product non-specific. Drug and product specific
22 parameters include parameters for drug substance,

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1 formulation characterization, and the in vivo
2 testing results. The drug and product non-specific
3 parameters are parameters used to establish the
4 relevant physiological system.

5 The physiological system can be the GI tract
6 for solid oral dosage forms or GI locally-acting
7 products, intranasal system for local or
8 systemically acting drug delivery, ophthalmic
9 system for ointment, lung for metered-dose inhaler
10 or dry-powder inhalers, and skin for patches,
11 ointment, and creams.

12 This slide summarizes some of the key roles
13 that a PBPK model has played for generic drug
14 development. It's been shown earlier by Dr. M.J.
15 Kim. And here, I just want to stress, for
16 locally-acting and the complex products, the color
17 highlighted in red is most relevant to complex
18 locally-acting products. Complex products defined
19 by complex routes of drug delivery or defined by
20 complex formulation such as the liposomes,
21 suspensions, emulsions, and gels.

22 A physiologically based model can help build

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1 critical quality attribute identification on a
2 model-based assessment of action site drug
3 concentration. There are increasing trends in
4 using PBPK models to support regulatory
5 decision-making in the realm of generic drug
6 development.

7 This slide has some of the PBPK modeling of
8 the drug delivery following oral route of
9 administration. I think enough has been presented
10 in the earlier presentations. I will skip it for
11 the sake of time.

12 This table gives the highlight of PBPK model
13 impacts in calendar year 2016, including example
14 drug and the specific contribution that the model
15 has made. They range from identification of
16 dissolution method, product quality control,
17 assessing risk following release mechanisms of
18 change for modified release products, assessment of
19 proton pump inhibitor effect, PK metrics
20 determination, assessment of alcohol dose dumping
21 risk, and the BE study design.

22 Of note, all of the decisions that a PBPK

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1 model have contributed has a direct impact on the
2 product approvability.
3 In the following slide, I will talk about
4 quantitative clinical pharmacology and its impact
5 in the generic drug development and review.
6 The most commonly used toolkit available in
7 quantitative pharmacology starts from new drugs,
8 and they can be shared between new drug and generic
9 drug development. For example, PK/PD modeling for
10 new drug development is also the key to advising BE
11 study design, sensitivity of PD endpoints-based BE
12 assessment.
13 Population PK can be used for model-based BE
14 assessment for drugs with sparse PK sampling. The
15 equivalent part of a clinical trial simulation for
16 generic drug development is virtual BE study.
17 What is a virtual BE study? It's the use of
18 a model to compare test and reference formulations
19 based on the computer simulations. The model must
20 have a formulation variable that can be adjusted to
21 represent a difference between test and reference.
22 The model generates a population for BE study and

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1 compares the test and reference product in that
2 formulation. We can simulate many studies to
3 estimate the probability of success and failure,
4 which we usually call the power assessment.
5 Quantitative clinical pharmacology is an
6 established and useful toolset for solid oral
7 products and applications. The key question and
8 challenge now is can we develop a further thought
9 on model-based drug development for locally-acting
10 and complex products?
11 This slide, I've shown earlier. It shows
12 the areas that quantitative clinical pharmacology
13 has contributed. The red color indicates the
14 application areas that are closely related to
15 complex or locally-acting product.
16 For locally-acting product, we always have
17 an interest in further abbreviating the program for
18 regulatory science research for model-based BE
19 assessment, and using appropriate PD endpoints or
20 biomarker which can be more sensitive to establish
21 BE and more sensitive methodologies for clinical
22 endpoint evaluation and assessment.

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1 For complex dosage form such as long-acting
2 injectables, models can be used to establish the
3 new metrics for BE assessment. For other
4 applications, pharmacometric tools have been
5 routinely used for NTI drug identification,
6 classification, and a PK metrics determination.
7 Applications of quantitative clinical
8 pharmacology in the realm of generic drug review
9 ranges from across PK metrics determination BE
10 study design, clinical endpoint evaluation, and
11 in vitro BE assessment.
12 This table summarizes what we have done in
13 the calendar year 2016. Here, I want to say that a
14 good modeler not only will have high technical
15 expertise, they are also good philosophers. They
16 are strategists. Before we do a model, we need to
17 think based on the data, based on the information,
18 based on the experimental result, in vivo/in vitro
19 studies, how do we want analysis, analyze data, and
20 what tool should we use, and what conclusions can
21 be safely drawn from the toolset.
22 I'm very glad that the division has

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1 assembled the key skillset and a bunch of brilliant
2 scientists in this area. Not only for PBPK, PK/PD,
3 we are also actively thinking of development models
4 that can be used to evaluate health outcomes and
5 big data. With the advancements of new technology,
6 information or data explosion is happening
7 everywhere. Motion learning is one of the most
8 popular techniques that enables data-driven
9 decisions into a process.
10 There's no difference from FDA. Currently,
11 the efforts are many within FDA. Big data models
12 have been exploited in the areas including but not
13 limited to the following: to predict work load, to
14 prioritize scientific research needs, identify
15 areas for healthcare cost reduction, and
16 opportunities for regulatory communications.
17 Under the GDUFA regulatory science program,
18 around 30 grants and contracts have been initiated
19 that are closely related to quantitative methods
20 and modeling. They mainly are partially fall into
21 subject areas such as further BE investigations,
22 identification of new BE metrics, PBPK models for

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1 systemic and locally-acting products, model-based
2 BE assessment based on PK or PD endpoints,
3 postmarket evaluation, and NTI classification.
4 These two tables summarize the 30 or so
5 grants and contracts. Given the time, I cannot go
6 through them one by one. Every one of these grants
7 and contracts are of high importance to inform our
8 internal regulatory decision-making.
9 Today, we should be more focused on the
10 further research needs to enhance the program. We
11 continue to face regulatory challenges from the
12 area of BE assessment for complex and
13 locally-acting product. Recent advancements in
14 science have created several innovative pathways
15 for BE of locally-acting products in addition to
16 clinical endpoint BE studies.
17 Specifically in combination with a broad
18 spectrum of in vitro/ in vivo testings,
19 quantitative methods and modeling is one of the key
20 toolsets. Model-based guidance development for
21 complex and locally-acting product will ensure
22 timely availability of high quality and affordable

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1 generics for patients.
2 The current research priorities from FDA
3 perspective includes the following: develop PBPK
4 models for complex routes of delivery, including
5 nasal, inhalation, dermal, ophthalmic where there
6 is limitations to generic competition; use
7 quantitative pharmacology and bioequivalence trial
8 simulation to optimize BE studies for complex
9 products; leverage big data for decisions related
10 to generic drugs.
11 For each of the priorities, the key
12 questions for input from the panel are
13 opportunities to use modeling to inform regulatory
14 decision-making in both pre-ANDA and the review
15 stages and gaps that need to be closed for
16 quantitative methods to provide evidentiary support
17 for drug approval especially for locally-acting and
18 complex products.
19 With that, I would like to thank everyone,
20 thank the panel and the audience, and looking
21 forward for more constructive discussion in the
22 following session.

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1 DR. CHOI: Our next speaker is Dr. Amitava
2 Mitra from Sandoz, who will provide the industry
3 perspective on generic drug research needs.
4 Presentation – Amitava Mitra
5 DR. MITRA: Thank you, Stephanie.
6 Thank you, all, for being here and for
7 inviting me today. I'm going to talk about or give
8 my opinion on the application of physiologically-
9 based PK modeling in generic drug research. Just a
10 disclaimer, it's my opinion, so hold me responsible
11 if you don't agree with anything.
12 This is a brief outline. I will just very
13 briefly go through some introductions. A lot of it
14 has already been covered in the previous
15 presentations and Liang, so I'll not belabor that
16 much.
17 I'm going to focus primarily on virtual
18 bioequivalence and where I think there is a lot of
19 room where this could be applied in generic drug
20 research particularly. I'll give two examples
21 where we have had success on virtual BE, one CR
22 example, and immediate-release example, and then

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1 conclude, and a slide on future use.
2 So before I get into modeling and simulation
3 and talk about that, modeling, as we all know, is a
4 pretty broad field, and terms are used
5 interchangeably. So I just wanted to make sure
6 that the audience understands what I'm going to
7 talk about today.
8 So what I'm going to focus on today is
9 particularly physiologically based oral absorption
10 modeling. We are not talking about DDI. I use
11 PBPK here, but it's not really full PBPK. We're
12 going to focus mostly on oral absorption model and
13 try to answer CMC questions particularly. So
14 that's the focus of my talk here.
15 This schematic is just to show that the kind
16 of information that we need to build these models
17 from the ground up, you need formulation, compound
18 information, some kind of a PK input, either
19 compartmental or PBPK if that's what you're after.
20 And then of course the GI physiology is very, very
21 important, and I'm going to talk a little bit more
22 on that as I talk about virtual BE.

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1 The outcomes can be on several fronts. You
2 can get the full PK profile. That's where the
3 virtual bioequivalence comes into play. We could
4 have fraction absorbed/fraction dissolved type
5 information if you're going up to IVIVC, especially
6 physiologically-based IVIVC, not numerical IVIVC,
7 and also regional absorption characterization of
8 the formulation.

9 If we're talking about controlled-release
10 formulation to understand where is the drug
11 actually absorbing and how can we tweak formulation
12 to change the absorption a little bit here and
13 there.

14 Again, from my perspective, we are talking
15 about trying to predict small changes in
16 formulation, slight variations in dissolution, and
17 predicting how did that affect PK. So it's pretty
18 complicated in my opinion, and we need these models
19 to be exquisitely sensitive to the slight changes
20 in dissolution that we want to predict and have an
21 effect on PK. And I thought these quotes pretty
22 much capture my thoughts here.

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1 But nevertheless, in the last decade or so,
2 a lot has been done in this area, both from
3 understanding the physiology perspective, and
4 Gordon and Jim already presented some of the nice
5 work that they are doing, a lot is happening in
6 various academic labs in Europe, trying to
7 understand the GI physiology. And also from the
8 software perspective, the vendors have done a very
9 nice job of incorporating all that data into the
10 model, but a lot needs to be done in that.

11 But nevertheless, a lot has happened in the
12 last decade or so, and especially from a CMC
13 perspective, we have seen examples of BE
14 predictions in the literature for, again, a
15 dissolution input and change how that affects
16 formulation performance, QBD applications, an
17 example on dissolution, food effect prediction,
18 DDI, especially with pH-reducing agents. I'm not
19 talking about enzymatic DDI, rather, it's a local
20 GI DDI.

21 More recently, on these complex
22 formulations, like amorphous solid dispersions,

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1 nanoparticles, et cetera, these are again extremely
2 complicated formulations, and we're trying to
3 predict a very complicated dissolution -- using a
4 very complicated dissolution and trying to predict
5 the effect on PK.

6 Nevertheless, the same thing, our regulatory
7 colleagues have also taken this up, and a lot has
8 been talked about today. This is obviously not a
9 laundry list, but some examples of where FDA has
10 published quite a bit on this. So it's very
11 heartening to see that it has been taken up not
12 only from the industry perspective and academia,
13 but also being used in regulatory settings where
14 obviously it matters the most from drug product
15 perspective.

16 So again, as I said, I'm going to focus on
17 virtual bioequivalence, and Liang already
18 introduced this topic. So I'll just skip that and
19 say, where do I think are the applications of
20 virtual bioequivalent?

21 So obviously, the idea is to predict outcome
22 of formulations changes on bioequivalence. That's

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1 a given. The first thing could be, if we have
2 enough confidence in these models and they have
3 been validated, et cetera, the immediate impact
4 could be, again, from a generic perspective, you
5 could reduce the number of pilot PK studies that
6 are run. Obviously, that has huge implications
7 both on the cost, and time, and also the ethical
8 implications of running these human studies
9 multiple number of times.

10 It will give us more confidence, obviously,
11 going into a pivotal BE study, again, assuming that
12 we have enough confidence in these models. And
13 another provocative idea would be that we would be
14 in a situation at some point of time where on a
15 case-by-case basis, we are able to waive these
16 pivotal BE studies. And I will show some examples
17 today. And obviously, we are not there yet, but
18 I'm pretty confident we'll get there.

19 I talked about this and touched on this a
20 little bit. The models themselves need a lot of
21 work still. Again, particularly when you're
22 talking about virtual bioequivalence, the first

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1 thing that needs to be done better is incorporation
2 of intrasubject variability. And again, some of
3 the work that is being done at Michigan and also in
4 various labs in Europe is working towards that, but
5 a lot needs to be done there.

6 It's not just generating that data, but we
7 have to work even with the commercial software
8 vendors to incorporate that into the model. There
9 are ways to do that now, but they are not perfect
10 by any stretch of imagination.

11 The other thing that comes to mind is the
12 colonic absorption model. Again, this is not ideal
13 where it is right now. And I bring this up because
14 I will show you an example of a controlled-release
15 formulation. And I'm sure folks here who have
16 worked on modeling controlled-release formulation
17 knows the colonic absorption models that are out
18 there right now -- and pick any software -- they're
19 not there. We have to change them as we go along.

20 Food effect is another one. Again, some
21 folks here might be aware. Sutton [ph] recently
22 published a very nice paper on low/high fat meal,

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1 and volumes, et cetera, bile salts. Again, those
2 kind of data are needed and needs to be
3 incorporated into these models, particularly if
4 we're trying to, again, model CMC effects,
5 et cetera. I will not belabor the point, but
6 needless to say, the models need work, but I'm
7 pretty hopeful we'll get there.

8 So moving on to the case studies, this is an
9 example of trying to predict how we are. We have
10 three test formulations. It's a controlled-release
11 formulation, BCS class 1 molecule and comparing to
12 a RLD which one of these would be the closest to
13 bioequivalence, to the RLD. Again, this is early
14 on in development, so it would be what we would
15 call a pilot stage.

16 The way this modeling was done -- again, I
17 don't have time to go into much technical detail
18 here, but you take this dissolution data, fit this
19 to a double Weibull function, and then build a
20 model. Obviously, in this case, in both the fasted
21 and the fed the model was okay from our
22 perspective. The fed, again, to be completely

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1 transparent, did need some tweaking on the
2 physiology part to get it to what I'm showing you
3 right now.

4 Obviously, this model, the single
5 simulations here do not give us any information or
6 much information about bioequivalence per se. What
7 we need for bioequivalence is basically population
8 simulation. We need to incorporate variability in
9 there because we are trying to predict the CIs,
10 which is most important. GMRs can only give you so
11 much information there if we want to be seriously
12 predicting bioequivalence.

13 So what was done in this particular case
14 was -- what I show here is 10 simulations with 25
15 subjects in a crossover manner. But a lot more
16 simulations were run, but at some point, you get
17 diminishing returns. So there's no point doing 100
18 simulations with 25 subjects if you can get away
19 with 10 simulations. But obviously, nobody can
20 predict that a priori, so that exercise has to be
21 done.

22 The other thing to note here, and I

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1 specifically put here, all this work was done in
2 GastroPlus. People who use GastroPlus know that
3 GastroPlus can itself predict whether you are
4 bioequivalent or not. I personally do not put much
5 stock in that. So what was done here is we take
6 those virtual simulation data, and the GMRs and CIs
7 were calculated outside of GastroPlus.

8 Here is an example. This is a fasted state,
9 so we have the three tests. And again, at least
10 directionally, it gives us the idea on which of
11 these formulations to take forward.

12 Now, if you look at the CIs, I did put the
13 CIs there, too. You can clearly see that they are
14 between the observed and the predicted, the CIs
15 are. Some of them are quite off, but at least,
16 directionally, it gives us some idea.

17 So this is where I say that capturing the
18 intrasubject variability in these models is just so
19 important. The same thing was done in the fed
20 state. Again, I don't have time to go into all the
21 technical details, but again, the fed physiology
22 was a little bit more complicated. But again, you

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1 see the CIs there. Some of them are not even close
2 to what the observed data was. So there are some
3 things that need to be obviously a lot more room to
4 improve there.
5 Finally, here is the "pivotal batch" and the
6 RLD. Again, the same thing was done. I'm just
7 showing you an example of the fasted state here.
8 You can create almost like a heat map. Run this
9 virtual trial and see how many times of these do
10 you fail and how many times do you pass.
11 In this case, it shows there are 3 out of 10
12 chances it will fail on Cmax and 2 out of 10
13 chances fail on Cmax. But it's probably a risk
14 worth taking, again, depending on the situation of
15 course; and then here, the model predictions and
16 the observed bioequivalence data. And in this
17 case, the model seemed to have done pretty well.
18 At least, it's predicted it's going to be
19 bioequivalent.
20 So that's an example of a controlled-release
21 formulation, and here is an example of case 2 of an
22 immediate-release product. This is etoricoxib, a

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1 BCS class 2 molecule, weak base, fairly highly
2 soluble, a typical weak base, very high solubility,
3 at low pH, and the solubility drops as the pH
4 increases.
5 Now, in this particular case, the struggle
6 that we faced was which dissolution is the most
7 predictive of bioequivalence? And the situation
8 that we were in, it was in a SUPAC. There was a
9 manufacturing site change, and multimedia
10 dissolution was done. And at 4 and a half and 6.8,
11 it was not F2. So obviously, we were stuck in a BE
12 situation here that we wanted to avoid.
13 Another thing to note here is etoricoxib,
14 even though it's a weak base, there is data that as
15 it goes from the stomach to the small intestine,
16 there is not much precipitation happening there.
17 So A, it's completely soluble in stomach, and B, as
18 it transits from stomach to small intestine, there
19 is not much precipitation.
20 So we were arguing that this high-pH
21 dissolution was overly discriminating. It is not
22 relevant from a bioperformance perspective. And we

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1 set about proving that through modeling. So we
2 obviously did a lot of work just building the model
3 against all available phase 1 data, different
4 phase 2 PK data, food effect, et cetera, and I show
5 you some example here of the model performance at
6 the high dose.
7 Again, we ran some virtual trials, and what
8 this model showed was that if we use the pH 4 and a
9 half and 6.8 dissolution, it will predict that it
10 will not be bioequivalent, although at pH 2, it
11 will be bioequivalent.
12 Again the argument that we were putting was
13 that 4 and a half and 6.8 pH is not biorelevant.
14 It is not biorelevant in this particular case.
15 Then nevertheless, we had to run the BE study, and
16 the BE study came out to be -- even with those F2
17 differences, the batches were still bioequivalent.
18 And the GMRs were in fact very, very tight.
19 So this is an example where, again, in this
20 particular case, pH 2 dissolution was the most
21 biorelevant, so this is an example of where
22 understanding what dissolution input is needed is

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1 pretty key for these bioequivalence predictions, of
2 course, otherwise, you can be completely misled.
3 So with that, just to conclude -- I think I
4 have two more minutes -- overall, the experience of
5 these models, specifically in the CMC area, has
6 been pretty robust, both in industry and in the
7 regulatory agency, although there's a tremendous
8 potential of these models in generic drug
9 development, specifically in virtual bioequivalence
10 setting.
11 I completely agree with Paul's statement at
12 the last panel that I think as a generic industry,
13 we need to be utilizing these models more. I think
14 there's a lot these models can help us with. I did
15 not talk at all about complex drug products, but
16 some things like long-acting injectables, again,
17 the models are being developed, so there's a lot
18 that can be utilized in that arena, too.
19 Finally, for future use, again, I took this
20 slide, and Rob was kind enough to let me use his
21 slide from the last AAPS. I think it pretty much
22 summarizes my thoughts to expanding BCS class. We

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1 had a lot of discussion about BCS class 3 waivers.
2 I think these models can be used a lot in those
3 cases if you are not Q1/Q2.
4 Again, in specific cases, even in BCS
5 class 2, I showed an example of etoricoxib. So
6 even specific cases in BCS class 2, I think with
7 enough work done, these models can be used.
8 Fed, I personally think we do way too many
9 fed BE studies, and some of them are pretty low-
10 hanging fruit that could be waived, and there are
11 others. Hopefully, we'll get to that during our
12 panel discussion. So with that, I will just end my
13 presentation and thank you.
14 (Applause.)
15 Public Comment Period
16 DR. CHOI: We will now begin the public
17 comment period for this session. Our first
18 presenter is Dr. Yu Feng from Oklahoma State
19 University.
20 DR. FENG: Good afternoon. Thank you very
21 much for giving me this opportunity to talk about
22 our research. So this talk is about testing the

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1 new targeted pulmonary drug delivery method using
2 computational fluid dynamics, fluid particle
3 dynamics method.
4 The motivation is straightforward, as
5 discussed by a lot of people today. Using modeling
6 saves time and money, and it's not non-invasive.
7 Also, using the CFPD method, it can provide high-
8 resolution results, so it can provide more
9 information to generate the physical insights.
10 Talking about the targeting, what we want to
11 achieve is to reduce the side effect, to enhance
12 the therapeutic outcomes. In that case, we can
13 control the particle trajectory by only
14 manipulating their release method.
15 I'll just skip the governing equations. So
16 conventional pulmonary drug delivery, when we
17 inhale the drugs, it can spread everywhere. What
18 we want to control the release. For example, in
19 this slide, we want to release the particles solely
20 in the yellow region, and most of the particles
21 will end up in the left upper lobe.
22 Another example is this one. If we release

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1 the particles in the green zone, most of the
2 particles will reach the right lower lobe. So in
3 this case, we can just manipulate the release
4 position of the particles, and we can achieve this
5 lobe-specific drug delivery.
6 So talking about this simulation, it is only
7 visible for that specific long-area geometries.
8 What we want to do to enhance the capability of
9 this simulation framework is to want to make this
10 work for at least the population.
11 So there are three works, we think, that are
12 necessary to further extend our simulation. The
13 first thing is about intersubject variability
14 study. That means that we want to have this CFPD
15 simulation with arrow bars, so we want to build up
16 a virtual population study, so in that case, it can
17 be a test whether it's feasible for the population
18 or somehow it can be restricted to a certain small
19 cohort.
20 The second thing we want to do is try to
21 extend the capability of the simulation. The
22 endpoint of the drug is not a deposition, but it's

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1 the other deposition dynamics. We want to see the
2 translocation of these drugs, so we want to combine
3 the CFPD model and the PBPK model.
4 A third thing is we want to generate a fast
5 and accurate tool to provide us with a precise
6 treatment plan, meaning that we have a patient
7 coming in, They have a specific disease, and based
8 on all the inputs they gave us, we can just
9 directly give them an optimized drug formulation
10 and optimized drug delivery method.
11 It's all about the big data and machine
12 learning. The data we viewed is based on our
13 simulation results using a CFD model. So this is
14 our virtual human, version 1, so this is something
15 we want to use for the subject variability study,
16 and this is all the geometries we have, upper
17 airways and long-airway geometry. So we can
18 combine different options, and we can generate a
19 virtual population.
20 The last thing is all about this multi-scale
21 modeling. So yes, thank you very much.
22 (Applause.)

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1 DR. CHOI: The next speaker is Dr. Scott
2 Mosley from the University of Florida.
3 DR. MOSLEY: Hi. Thank you for the
4 opportunity to share our thoughts with you today.
5 I'm briefly going to explain -- really, this is my
6 only slide. It's just the title of our current
7 FDA-funded project, Open-Labeled Pharmacokinetic
8 and Pharmacodynamic Studies in Metoprolol ER.
9 This is briefly one of the recommended
10 studies by FDA specific from metoprolol succinate
11 formulations. If you don't get the waiver, this is
12 what they would suggest you do to show
13 bioequivalence.
14 So we're conducting this, just normal PK and
15 the PD part, a 24-hour ambulatory blood pressure,
16 Holter monitor for heart rate, and a smart pill
17 that they ingest, which reports pH, pressure,
18 temperature, and time.
19 I don't have any data to show because it's
20 still ongoing, but just clinical observations, I'm
21 working as the research pharmacist on the project.
22 We have noticed some things that are generating our

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1 next round of grant writing and ideas to share.
2 So we've noticed there are similar blood
3 pressures between the formulations, which is
4 expected, but we're noticing possible differences
5 in heart rate. So something to focus on, not
6 necessarily blood pressure anymore, is beta
7 blockers are no longer first-line per JNCA [ph] a
8 couple of years ago, but they are still first-line
9 in heart failure.
10 Another is the emerging data on these
11 inactive ingredients, in particular HPMC,
12 hydroxypropyl methylcellulose or hypromellose. And
13 it may have an influence on metoprolol ER release
14 characteristics, as shown by some of this PBPk
15 modeling.
16 With the heart failure model, we feel like
17 that would be more important moving forward as the
18 metoprolol ER product is superior to the IR
19 product. This is a special situation where that
20 has been shown, and it's due to the release
21 characteristics of the drug, which are very
22 important, that you may not see when looking at it

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1 in vitro. But in vivo, it changes the heart rate
2 variability.
3 So using those ideas, we have mainly two
4 suggestions for possible research, one being this
5 marriage of the translational research between PBPk
6 modeling findings with in vitro and in vivo being
7 the clinical trials. So we could focus right now
8 on this HPNC and see if these PK models are
9 predictive of what we see in vivo and in our
10 clinical setting. And that's particular for
11 metoprolol ER.
12 The second would be to still keep an eye on
13 the influence of clinical efficacy in ER
14 formulations rather than give the waiver, focus on
15 this type of situation, where ER products are
16 superior to the IR products, like the case of
17 metoprolol in heart failure. Thank you.
18 (Applause.)
19 DR. CHOI: Our last presenter is Dr. Kenneth
20 Morris from Long Island University and also
21 representing NIPTE.
22 DR. MORRIS: Thank you. I'm batting

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1 clean-up again. Today, I just wanted to talk real
2 briefly about a proposal that's currently part of
3 EO1 in front of FDA called New Prior Knowledge.
4 And basically, the idea is that drugs that are
5 coming off patent now, that might be developed as
6 generics, were studied, and studied years ago with
7 techniques that may have advanced or may have
8 changed.
9 Also, there are drugs that already off-
10 patent that are not being developed as generics
11 that should be. Janet Woodcock testified that
12 there were some 1800 such compounds, and some of
13 them may not be developed because of financial
14 issues, but many of them because of technical
15 issues.
16 So what's really needed is a public
17 knowledge base to provide information for all
18 contenders to get this backlog of compounds started
19 down the path, as well as to reduce cycle times and
20 to take care of the out-of-date characterization.
21 The new prior knowledge is sort of an
22 acronym -- or not an acronym, but NPK is the

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1 acronym for New Prior Knowledge that basically says
2 that there are compounds for which the information
3 needs to be generated now so that companies unable
4 to marshal the resources against the projects can
5 have access to it. It seems pretty obvious to us,
6 of course.
7 So the end result of that I've outlined
8 here; I won't go through this slide. But the end
9 result of that could be something that would be
10 something like NIPTE monographs, if you will, that
11 would be generated by the collaboration of the 17
12 departments, and schools, and different
13 universities working on these projects or, and/or I
14 should say, knowledge bases that will be available
15 to companies that are wishing to develop such
16 compounds.
17 A recent poll that Ajaz Hussain just shared
18 with us is that 90 percent of Americans,
19 Republicans, Democrats, Independents, Anarchists
20 all favor measures to promote generic product
21 development. So this is not partisan. It's not
22 controversial. It just needs to be done.

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1 As I said, this is part of EO1 that,
2 actually, Steve Byrn is leading that has been
3 submitted and is in front of FDA. You can think of
4 New Prior Knowledge as a Lexus-certified pre-owned
5 car. So it's not that it's not vetted. It's
6 vetted very well, but it's information in a context
7 that wouldn't have otherwise been available. Thank
8 you.
9 (Applause.)
10 Panel Discussion
11 DR. CHOI: I would like to thank all the
12 speakers and all those who have presented comments
13 during the public comment period. We will now be
14 starting our panel discussion, and I just wanted to
15 remind all the panel members to please speak
16 closely into the microphone, and also for any
17 members of the audience who will be participating
18 in the panel discussion also to speak closely into
19 the microphone as well as announcing your name and
20 your affiliation before you present your comment.
21 Before we begin, I'd like to now ask each of
22 the panel members to state their name and

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1 affiliation, starting with Dr. Ethan Stier.
2 DR. STIER: Hi. My name is Dr. Ethan Stier.
3 I'm the director of the Division of Bioequivalence
4 II, Office of Bioequivalence, Office of Generic
5 Drugs.
6 DR. AU: I'm Jessie Au. I was a professor
7 of pharmaceuticals at Ohio State for 30 years, and I
8 traded that job for four. So I have three jobs in
9 academia, where I spend about 60 percent of my time
10 to develop a new program, a system-based modeling
11 approach to help drug development. This includes
12 two endowed-chair professorships at two
13 universities. The rest of the time, I'm a CSO of a
14 clinical-stage biotech.
15 DR. CONNOR: I'm Dale Connor, director,
16 Office of Bioequivalence in OGD in CDER.
17 MR. DiLIBERTI: Charlie DiLiberti, an
18 independent consultant with Montclair
19 Bioequivalence Services.
20 DR. GROSSER: Stella Grosser. I'm with the
21 Office of Biostatistics in the Office of
22 Translational Sciences in CDER, FDA. I'm a

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1 division director for DB-VIII, which is the group
2 of statisticians that support OGD.
3 DR. HOCHHAUS: I'm Guenther Hochhaus with
4 the University of Florida.
5 DR. MITRA: Amitava Mitra, clinical
6 development, Sandoz.
7 DR. POLLI: James Polli, University of
8 Maryland.
9 DR. ZHAO: Liang Zhao, division director,
10 Quantitative Methods and Modeling, Office of
11 Research and Standards, OGD.
12 DR. TSANG: Yu Chang Tsang, chief scientific
13 officer in biopharmaceutics and biostatistics at
14 Apobiologix, division of Apotex.
15 DR. YIM: Hi, Sarah Yim, director of the
16 Division of Clinical Review in the Office of
17 Bioequivalence, OGD.
18 DR. ZHAO: Ping Zhao, pharmacometrics,
19 Office of Clinical Pharmacology, FDA.
20 DR. LIONBERGER: Rob Lionberger, director,
21 Office of Research and Standards, OGD.
22 DR. SEO: Paul Seo, director of Division of

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1 Biopharmaceutics, Office of New Drug Products,
2 Office of Pharmaceutical Quality.
3 DR. CHOI: Thank you. The first priority
4 area that we would like to receive input relates to
5 the development of PBPK models for complex routes
6 of delivery such as nasal, inhalation, dermal, and
7 ophthalmic routes where there are limitations to
8 generic competition.
9 I'd like to ask Dr. Jessie Au to start us
10 off on providing comments regarding challenges as
11 well as new approaches or strategies in PBPK
12 modeling for these locally-acting products.
13 DR. AU: Yes. I was listening all day, and
14 I was thinking about how some of our own work and
15 the lessons that we have learned would apply here,
16 especially for the locally-acting drugs, and also
17 looking forward to the future, where you're going
18 to have lots of new cancer drugs that's coming off
19 patent because in the oncology field, there have
20 been a large number of drugs approved in the last
21 10 or 15 years.
22 So I think all those point to one thing,

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1 that we may want to look into supplementing PBPK.
2 So in my entire career, I've been developing drugs
3 for locally acting, so mainly for organ-confined
4 diseases in bladder cancer, prostate cancer, and
5 now peritoneal cancer. So in our case, we actually
6 want not to leave the locally-acting site. So
7 we're dealing with the same problem you are faced
8 with.
9 Now, the other thing we also do in cancer is
10 a little bit more complicated than other organs
11 because cancer is not normal. It's not natural.
12 Its development is chaotic. The blood circulation
13 is very chaotic. There's a lot of spatial
14 heterogeneity.
15 So how did I extrapolate that to the
16 question you asked about locally-acting drugs? One
17 thing we had to deal with in our case was to be
18 able to predict from compartments where we can
19 sample, and now to be able to predict the
20 concentration of drug and time profile as a
21 function of space, so the distance it traveled, how
22 does a drug travel from point A to point B? What

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1 are the chaotic systems we encounter? What is the
2 extracellular matrix we have to deal with?
3 So at the end, instead of using a
4 probabilistic approach like PBPK, we actually are
5 using a deterministic approach. So we are
6 pinpointing a point in the site where you want to
7 know where the concentration is.
8 I think that type of approach, which is
9 loosely called multi-scale models, can apply in
10 locally-acting agents, And it also would apply in
11 cancer drugs that you're going to be dealing with,
12 because a lot of those are large molecules. The
13 transfer's going to be very difficult to deal with.
14 You cannot take one generic versus the innovative
15 drug. It's more complicated than small molecules.
16 I hope that's clear.
17 DR. CHOI: Any other comments from the
18 panel?
19 DR. ZHAO: I just want to follow up with
20 Dr. Au's comment. You mentioned a sample drug for
21 PK measurement from accessible parts. So does that
22 refers to the action set or some other site that is

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1 maybe a surrogate organ for the --
2 DR. AU: Very good question. Thank you,
3 because this is hard to explain in just a few
4 sentences. So I'll give I think now the best
5 example that I have. I'm sorry. I back up.
6 There's a better example, work that I had done
7 about 30 years ago in bladder cancer, where we
8 basically predicted concentration at tumor, where
9 we don't even know here they are. But we predicted
10 concentration, we synthesized the phase 3 protocol,
11 and we did a phase 3 trial. And now prediction
12 came out right on the money.
13 So that gave us the confidence that you can
14 actually predict a concentration in spatial, rather
15 than just by time. So that's one example.
16 The other example, I am about to do a
17 clinical trial, so I can tell you soon whether it
18 will work. This one is a little bit more
19 complicated. This is peritoneal cancer, where we
20 put a drug in the peritoneal fluid.
21 So we can tap the fluid; we can measure
22 that. We can also measure the blood concentration.

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1 So by having the two compartments on two sides, I
2 can predict what's in the middle. And of course,
3 the more constraints you put on the model, the more
4 likely your model is going to be correct. So in
5 animals, we've proved we can predict the
6 concentration as the drug enters the tumor as a
7 function of distance, so that space on sampling the
8 peritoneal cavity and the blood.
9 Now, the bladder cancer situation is
10 actually similar. We just sampled the urine
11 because that's the most easy one. The drug never
12 enters the blood, just like what you have in your
13 locally-acting drug situation.
14 DR. CHOI: Any other thoughts on this
15 priority area?
16 DR. POLLI: Yes. Just maybe point out the
17 obvious. Dr. Zhao and Dr. Mitra, the two speakers
18 were incredibly harmonious on the issue of, yes,
19 this seem to be very, very important.
20 In terms of just my own background as an
21 academic, I would just add that it's extremely
22 difficult to understand how these more complex

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1 products work, even remotely, without actually
2 someone really going out of their way and studying
3 it. So to me, this is just an obvious big
4 priority.
5 DR. LIONBERGER: One thing we heard in the
6 morning session, and where I think it's an
7 important application of these, is that for a
8 certain subclass of these locally-acting products,
9 you can measure systemic PK levels if you think
10 that that's going to be something you wanted, and
11 then say, well what does that observation tell me
12 about the local concentrations?
13 I think a model that captures your
14 understanding can really be very useful for telling
15 about -- like, for example, if I look after
16 inhalation results, I can say, is there any
17 possibility that looking at the PK profile tells me
18 where in the lung it went, depending on how I know
19 that drug is absorbed or looking at a drug that
20 passes through the different layers of the skin.
21 So I think there's opportunities there in
22 certain situations to use these models to link to

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1 interpreting different types of information that we
2 see, that maybe are alternatives to these
3 insensitive clinical studies.
4 DR. HOCHHAUS: In the area of inhalation, my
5 personal case, modeling has helped me to understand
6 just much, much better what is going on or what
7 might be important. And it also has helped me to
8 maybe identify parameters that will mirror
9 potential differences in the lung.
10 As you said, can systemic PK be a mirror for
11 potential differences at the site of action? And
12 for me, modeling has helped that quite a bit, and
13 you can then also in the next step ask questions,
14 if there is a certain difference maybe in vitro
15 properties, what kind of effect would that have on
16 the situation within the target organ and how would
17 that then further be shown downstream.
18 So from that point of view, modeling has
19 helped me quite a bit and maybe also to find
20 arguments to find to say, yes, certain parameters
21 that we're going to monitor will potentially
22 reflect differences at the site of action.

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1 DR. LIONBERGER: Yes. I mean, another
2 example that you saw is what Bob Bellantone has
3 talked about, but you put an ophthalmic drop and
4 it's reduced and cleared down to a thin film.
5 For me, that's a problem in fluid mechanics
6 and computational fluid modeling to say how fast
7 the drops stay there. And that's a testable
8 prediction. You can look at the drop and see how
9 thick your film is. So if you generate testable
10 predictions, it really helps understand how
11 formulations distribute across some of the local
12 routes as well.
13 So it's not just the PK aspects of modeling,
14 it's really both the formulations and the
15 physiology aspects of these types of routes. And
16 they're complicated. You look at the pictures we
17 saw of the lung generation model. We funded
18 research in that area as well to build better
19 models of generation after generation of lung
20 branching to predict where drugs get deposited as
21 well.
22 So it's more than just the PK

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1 interpretation. There's lots of the physiology and
2 formulation interaction you have to capture here.
3 So here it's a research frontier. It's much less
4 established than the oral routes of administration.
5 DR. AU: I think the CFD, the computational
6 fluid dynamics, are especially useful when you
7 start doing multi-scale models, when you can
8 actually take one scale and separate it into
9 different compartments, and then start feeding
10 whatever fluid dynamics you want to do.
11 So I think what Rob said there, I think
12 that's something we in pharmaceuticals have not used
13 as much. And I think Stella mentioned at one point
14 that this is where we reach out to chemical
15 engineers and learn from them, and then help us in
16 this direction.
17 DR. CHOI: Thank you. I will move us to the
18 next priority area, which relates to the use of
19 quantitative pharmacology and bioequivalence trial
20 simulation to optimize bioequivalent studies for
21 complex drug products.
22 I'd like to ask Dr. Yu Chang Tsang to

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1 comment on this topic and the opportunities
2 available to use modeling to inform regulatory
3 decision-making during the generic drug review
4 process.
5 DR. TSANG: Thank you. This morning, we
6 heard that there were very few generic products
7 approved for complex drugs, and they have a good
8 reason for that, because the requirements are very
9 stringent. And I'm very happy to hear that the FDA
10 is open for a different means of demonstrating
11 bioequivalence because I think this could be very
12 important to generic industry in the following main
13 areas.
14 We heard that, for certain complex drug
15 products, we can use in vitro testing in some
16 situations with also PK bioequivalence to assure
17 for better equivalence, but for certain complex
18 drug products where clinical endpoint studies are
19 required, I think modeling and simulation can be
20 very useful for helping to reduce variability, the
21 high variability that can be observed in clinical
22 endpoint studies.

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1 We heard products this morning like
2 acyclovir cream, cyclosporine products, ophthalmic
3 products. Their products have very marginal
4 efficacy, so if one is to design a clinical
5 endpoint study on those drug products, it can be
6 very challenging with respect to the definition of
7 the equivalence criteria because those products
8 have so marginal efficacy.
9 If you try to apply the traditional 80 to
10 125 percent equivalence margin, one will find their
11 sample size can be extremely, extremely large. It
12 could be in the hundreds of thousands of patients.
13 And that can really create a hardship for generic
14 companies to conduct a clinical endpoint study in
15 order to demonstrate equivalence to the innovator
16 product.
17 In situations where the variability of
18 clinical endpoint studies is associated with the
19 design, perhaps we can also use simulation and
20 modeling to develop a design that can reduce
21 variability of the study. For example, for inhaled
22 corticosteroids, the proposed design is based on a

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1 parallel design.
2 Perhaps we can consider looking at using a
3 crossover design. Can we use simulation and
4 modeling to allow us to establish a design based on
5 a crossover design such that variability associated
6 with the endpoint can be reduced. As you know,
7 currently, with the parallel design, again, we need
8 hundreds of subjects to demonstrate equivalence for
9 FEV1 for inhaled corticosteroids. So I think that
10 is another area perhaps that modeling and
11 simulation can be used.
12 For other complex stuff like the long-acting
13 injectables, perhaps we can also use modeling to
14 determine what truncated area can be used instead
15 of doing a very, very, very long study. With a
16 truncated area, we can shorten the study. And
17 again, with the study being shortened, we can apply
18 a crossover design to reduce variability. So
19 that's another area where perhaps simulation and
20 modeling can be very useful.
21 We talk about NTI drugs. Currently, the FDA
22 guidance requires the use of reference scaling for

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1 bioequivalence of NTI drugs. And the reference
2 scaling needs to be applied even when the
3 variability of the reference product is very low.
4 The question is, when the intrasubject variability
5 is as low as 5 percent, the reference scale
6 criteria can be very, very narrow.
7 When different lots of the reference product
8 can differ in their drug content by up to
9 5 percent, is it necessary, is it perhaps a
10 necessary stringent to apply the reference scaling
11 down to that level when the lot-to-lot variation of
12 the reference product can be as high as 5 percent.
13 Perhaps we can use modeling and simulation
14 to assess the developments of the application of
15 reference scaling when the variability is so low.
16 Thank you.
17 DR. CHOI: Any other comments, Jim?
18 DR. ZHAO: Just quickly in response to Yu
19 Chang's comment, I think it's a really good
20 comment. And I just want to briefly say that we
21 welcome industries, too, if you have good thinking
22 of whether applying innovative approach or

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1 quantitative methodologies in the drug development
2 program, you are welcome to include that in the
3 package in the pre-ANDA interactions or even in the
4 application itself. I think there is a broad array
5 spectrum of modeling impact we can make in making
6 safe but effective generic product with the public.
7 But having said that, our general
8 expectation, as also elaborated by Dr. Dale
9 O'Connor from the last panel discussion that the
10 model needs to be qualified, verified for the
11 purpose of the use. Depending on the application
12 purpose, you may have a high barrier for
13 qualification or a low barrier for qualification.
14 It also relates back to the comment Dr. Raw
15 raised at the very beginning saying if we have some
16 observations that can be used to validate the
17 model, then that give regulatory agency very high
18 confidence in accepting the proposal.
19 We are modelers. We are also strategists.
20 We really want to have decision-making, but with
21 solid evidence. The model can be used to sometimes
22 replace part of the clinical endpoint study, but it

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1 can be used to -- previously, you only analyzed
2 data at a single time point, but if the
3 longitudinal analysis can allow you to reduce the
4 size of the trial, then we welcome all those ideas.
5 DR. CHOI: Jim?
6 DR. TSANG: I'm very glad there's an opening
7 for that. I remember several years ago when we had
8 to file control correspondence, it took years,
9 years of waiting before we can hear any response
10 from the FDA. So I'm very glad again to know that
11 there is an opening for Pre ANDA discussion. I
12 mean, that will certainly help the industry a lot.
13 But I think FDA is in the best position to
14 use modeling, because you have access to data from
15 the new drug side, which generic companies will not
16 have. And to me, you are in the best position to
17 look at modeling.
18 DR. CHOI: Jim, do you want to make your
19 comment?
20 DR. POLLI: The same comment as far as
21 impact, not so much relying on new drug data,
22 though. But Dr. Zhao kindly sent me his slides

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1 ahead of time, and I'm just noticing the highlights
2 of quantitative clinical pharmacology impacts. And
3 it's just nice to know when it has been
4 successfully used.
5 Also, in looking at this, I was thinking of
6 what I heard in Dr. Amitava Mitra's talk. As a
7 representative from I think a generic company, he
8 seemed to really like the fact that you are
9 advocating modeling. And what was going through my
10 mind was he must have a hard time -- not
11 necessarily him, but hard time convincing his
12 administration that there's some value in modeling.
13 So I guess my main point is it's probably
14 nice that you're promoting this because it really
15 helps people make the case that, yes, there really
16 are real examples, slide 18, where it could be
17 helpful for a generic manufacturer.
18 DR. LIONBERGER: I'd like to ask the
19 industry representatives a question. In this
20 question, you're talking about, before you do it,
21 especially these expensive large -- I'm thinking a
22 clinical endpoint study or a long-acting

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1 injectable, a six-month PK study.
2 How much modeling and simulation do you do
3 to estimate your risks of success or failure? In
4 some sense, I think that's not really visible to us
5 externally.
6 So I'm curious. If you're able to talk
7 about any examples that in your internal process,
8 that you are using these tools to gauge the risks
9 of the studies that you're doing. And if so, then
10 I think you'd be interested in generally improving
11 those tools to make better estimates of all the
12 risks and benefits of the studies that you're
13 taking. But I'm interested to hear what you're
14 able to say about those uses of modeling and
15 simulation.
16 DR. AU: At this moment, I'm still only
17 working with innovative drugs, but we use it all
18 the time, even protein binding, how much drug is
19 left. But I do want to come back -- I forgot who
20 said in the last session.
21 Every time we do a model, we predict
22 something, and we went back into the lab. And

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1 using only the most critical data points, we
2 identified critical attributes, what will cause me
3 most variation in vivo, then we go back and check.
4 So it's modeling, but it's really helping us
5 to find out more about the system because, as you
6 know, when we go to phase 3 trials, if you have
7 49.9 percent patients respond, then we fail. So
8 it's very critical that we find 50.1 percent of
9 patients that will respond.
10 So we are doing that a lot. I can't speak
11 for others, but I know because my lab has always
12 been very modeling centric.
13 DR. TSANG: We are envisioning using
14 modeling to predict outcome, but probably not
15 enough. I think the main reason is we're not sure
16 that can be useful. Again, FDA can take a very
17 informed role here, take the leadership role. If
18 generic companies are seeing more and more that FDA
19 is also using modeling and simulation, I would
20 think that industry will use it more often.
21 DR. CHOI: Charlie, did you have a comment?
22 MR. DiLIBERTI: When you power a

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1 bioequivalent study, you typically make the
2 assumption that the true population test to
3 reference difference or ratio is within about 5 or
4 maybe 10 percent, and you know that with 100
5 percent certainty. Modeling doesn't get you even
6 close to that kind of precision, so it has limited
7 utility in terms of predicting the outcome of a
8 bioequivalent study.
9 Now, from a new drug development situation,
10 where you're good if you're within plus or minus
11 50 percent, yes, that's great.
12 DR. CHOI: Siva and then Amitava?
13 DR. VAITHIYALINGAM: This is Siva
14 Vaithiyalingam from Cipla. We found modeling is
15 pretty expensive. We found modeling is pretty time
16 consuming. So what we found is relying on the
17 prior knowledge literature search, that gives ample
18 amount of knowledge to work on during the trial and
19 experiments, maybe small pilot studies.
20 So we rely mostly on those aspects that are
21 going on in the modeling. I'm speaking from a very
22 general perspective, not a one-company perspective,

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1 because I've worked at a few companies, so it is my
2 collective understanding of how industry does it.
3 DR. LIONBERGER: But don't you think the
4 idea of a model is your model represents what our
5 current knowledge is? So if we have a good model,
6 it represents what we know in an accurate, concise,
7 and generalizable fashion. So I wouldn't say, oh,
8 I use prior knowledge; I don't use models. I think
9 you're missing some opportunities.
10 DR. VAITHIYALINGAM: Rob, you are right.
11 But the thing is, the prior knowledge, and a trial,
12 and our experiments, it shows your direction of
13 where you are heading. But if I have to use a
14 model, my only concern is, I have to invest a lot
15 to make sure the predictability of the model is as
16 good as I would like to see.
17 It's a shift in the mindset, but still I am
18 not sure that I would agree at this point that
19 modeling is as good as -- or it can be made as good
20 as the prior knowledge, or use the modeling in the
21 place of prior knowledge and trial, and run
22 experiments.

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1 DR. CHOI: Amitava and then Aloka?
2 DR. MITRA: I have a few comments here
3 because it went from Rob's question to completely
4 diverging to something else, so I want to touch on
5 all of them because I feel pretty strongly about
6 all of those things.
7 So if I go back to Rob's initial question,
8 you used an example of long-acting injectable.
9 Again, my experience has been that the PBPK models
10 are not developed enough, particularly from a
11 physiology perspective. Immune response and the
12 site of injection, et cetera, I don't think the
13 models are there enough from a PBPK perspective,
14 although there is some work happening.
15 Personally, we have been using mostly IVIVC
16 for that kind of in the long-acting injectable,
17 although it is a pretty interesting area to work on
18 and a lot can be done just from a physiological
19 perspective if you want to build on a PBPK model
20 for long-acting injectables.
21 Going back to the application of modeling
22 and the comment that was just made, I think it

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1 comes a lot to just developing the skillset. I
2 think it's not fair to just blanketly say that the
3 models don't work, and I feel very strongly about
4 that. At least in the oral field, I think the
5 models are pretty developed. Are they 100 percent?
6 No. They are not. But they are in a situation
7 where it can be used pretty robustly and routinely,
8 even in regulatory submissions.
9 So I would very strongly push back on
10 comments that they don't work or we cannot power
11 studies based on modeling. I just don't believe
12 that's true. I'll just stop there.
13 DR. SRINIVASAN: Hi. This is Aloka
14 Srinivasan. Actually, I was almost going to say
15 something similar to what Amitava was just saying
16 to start with, that there are areas where there
17 aren't enough models developed. And the problem
18 with generics -- again, I think I'm going on saying
19 this -- is it's a race against time.
20 You can develop a model, and then go and do
21 everything; and in the meantime, somebody could
22 just do a pilot PK followed by the original study

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1 and bring the drug to the market. So now, you have
2 a fantastic drug developed and all this model, and
3 nobody to buy it, basically.
4 So these are some practical problems that
5 the generic industry is facing. Again, new drugs
6 do not face this. In most cases, they can develop
7 it at their own time.
8 This is where FDA helping us or hand-holding
9 us a little bit can be extremely useful. And we
10 would like to go that way, but we want to know that
11 what we are doing will be acceptable because,
12 again, it's all a question of time and a shoestring
13 budget, basically. Thank you.
14 DR. SEO: I just have a couple quick
15 comments also to address a wide variety of things
16 that have been said. The first is, I think it was
17 Dale and maybe someone else over there that had
18 mentioned with regards to modeling being this kind
19 of magic bullet savior in lieu of BE testing.
20 I completely agree with that. It's not a
21 magic bullet yet. Maybe someday in the future, I'm
22 long past dead and our grandchildren are some stark

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1 utopian future, they have that ability. But right
2 now, modeling is nowhere near there. And no
3 two-way crossover study, double-blind placebo-
4 controlled, yes, absolutely, the data is better
5 than a model in its current state.
6 Now that doesn't mean, though, that we
7 shouldn't try. There are benefits to doing a
8 model. Currently, as it stands, at least in the
9 quality realm, that model is supplemental and not
10 pivotal. So it supplements the data that we're
11 already getting to support your inevitable
12 post-approval change for a manufacturing site
13 change, or changing an excipient, or whatnot.
14 That PBPK data or whatever other modeling or
15 push that you're using is supplementing that
16 information, or borderline on the decision as it
17 often is, and that will help push us in the right
18 direction and give us a little bit more confidence
19 in our decision-making.
20 With regards to -- I think it was the
21 gentleman from Cipla, with regards to modeling,
22 it's time consuming, expensive. It is. But I

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1 think that, as Rob said, there is a missed
2 opportunity there with regards to doing that
3 modeling up front. Again, inevitably, there will
4 be some kind of manufacturing change, or a site
5 change, or maybe something even more disastrous
6 than that, where you have a CRO that's in trouble,
7 and everything at that site is now shut down.
8 Well, a lot of times, the first thing that's
9 asked is, what data can we save? What's the
10 quickest thing that's available, dissolution
11 testing, some kind of in vitro release test? And
12 if you have that model in place, that will answer
13 some questions versus just immediately pulling
14 everything off the shelf.
15 So I think there is some utility in putting
16 that investment first; you got to pay to play kind
17 of mentality. So I just wanted to address that as
18 well. Thank you.
19 DR. AMIDON: I think we need to --
20 DR. CHOI: Could you state your name and
21 affiliation?
22 DR. AMIDON: Gordon Amidon. I think we need

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1 to parse the term "model" a little more carefully.
2 I think, often, the problem with the model is the
3 input, the initial condition, not the actual
4 structural model, although that needs to be refined
5 to.
6 I think Amitava gave a very nice
7 presentation. I agree with you completely. The
8 USP dissolution methodology doesn't help you at all
9 because it's not in vivo relevant. So if you got
10 bad input, you're going to get bad output.
11 So I think it's maybe not the model that's
12 the problem. It's the initial condition.
13 DR. CHOI: Guenther?
14 DR. HOCHHAUS: I just want to also stress
15 what Dale said, that simulation alone will not be a
16 substitute for bioequivalent studies, but it can be
17 tremendously helpful, I think, in showing
18 bioequivalence that can start from making the
19 formulations/device; asking the question if I have
20 certain geometric constellations, would that might
21 eventually have an effect on the dose or the
22 regions where it will be deposited if I am thinking

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1 still inhalation.
2 It can be very, very helpful in either
3 identifying maybe alternative test methods, where
4 you can just use clinical trial simulations and
5 maybe show and convince people at the FDA, if we
6 design that study in such a way, it will be much
7 less expensive, we need less numbers, and the
8 variability will be smaller.
9 The thing that's also very, very, very
10 important in argumentation with the agency is if,
11 for example, a question comes back, quite often you
12 can answer those questions. If you have good
13 models, you can answer those questions with models
14 other than doing another study. And sometimes,
15 it's successful, and sometimes, it's not. But
16 sometimes it is. And I think modeling can help
17 that tremendously.
18 DR. CHOI: Dale?
19 DR. CONNER: I'd like to just give a brief
20 response to a comment that was made about eight
21 people back, that FDA is in the best position
22 because we kind of see all the data.

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1 There's some truth to that, but there are
2 many people, or quite a few people at this table,
3 not only FDA -- and FDA sees a certain view of the
4 data. We see a lot of people's data, but it also
5 is kind of filtered in a way. Now in ANDAs, we
6 some failed studies. We see some extra studies
7 that we never saw in the past.
8 But still, we don't see the studies where a
9 company has made a formulation and it's just a
10 total bust. They do this study, they get a lot of
11 data, didn't work, they have to start again, and
12 they go through. We never see that. So we're not
13 fully informed of what changes or different
14 strategies to design a product are successful and
15 what are not.
16 Others at this table, namely the sponsors,
17 see their own studies. And if you're a fairly
18 large sponsor, you see probably quite a few.
19 You're trying to develop multiple products over a
20 number of years. You're commissioning studies. So
21 you see it from a certain view, and you see some
22 things probably the FDA doesn't.

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1 The CRO industry and the consultant industry
2 sees a cross-section of those. They're called in
3 for different companies to do work and to design,
4 so they see a different view and see a lot of
5 studies that the individual sponsors don't see and
6 the FDA doesn't see.

7 So it's like putting a puzzle together. FDA
8 has a lot of pieces, but they don't have the entire
9 puzzle. Another group has some of the remaining
10 pieces, but they have some overlap with what we
11 have and so forth. And to put the puzzle together
12 completely, you need data from a variety of
13 sources.

14 So if your approach to this is, FDA is going
15 to do it for us because they have all the data,
16 that's really kind of naïve. Everyone has
17 important data and important things to contribute,
18 and nobody has it all, not even FDA. So to get the
19 so-called perfect model, if one can even define
20 that, there's going to have to be a lot of input
21 from a lot of different sources.

22 Nobody has it all, nobody has all the

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1 insight, all the data, or has seen everything, and
2 it's very hard because all of us, all those people
3 that I mentioned, have restrictions on what they
4 can do, what they can reveal to others, and so
5 forth. The FDA has restrictions. CROs have
6 restrictions. The companies certainly have
7 restrictions. They don't want their intellectual
8 property revealed to a competitor or to the public
9 maybe.

10 So everyone has restrictions, but everyone
11 has data that the others don't, and it's all
12 useful. So don't just assume the FDA is going to
13 do it all because we know it all because,
14 obviously, we don't.

15 DR. CHOI: Last comment, and then we move on
16 . Could you state your name and affiliation?

17 DR. VELAGAPUDI: This is Raja Velagapudi
18 from Sandoz. I wanted to come back to Rob's
19 question to input. One of the industry's
20 perspective is where should the FDA put the money
21 into in this research.

22 On the modeling issue, what Gordon said is

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1 100 percent true. First, figure out how to get the
2 discriminatory methods of release or identify
3 critical parameters for the long-term and complex
4 products. So priority one.

5 Generate the tests that discriminate, like,
6 5 to 10 percent difference, like for these
7 long-term injectables. And once they come to that
8 testing, then you have that discriminatory test of
9 release or critical parameters that you can
10 actually tie into the in vivo performance. Right?

11 So that is the input for the modeling. So
12 the modeling then takes on the physiological box,
13 this box, actually, you generated from the previous
14 experience. The input then goes into there. Then
15 you have an output. Then you see whether that
16 sensitivity is enough, like what Charlie is
17 bringing up. Then that will give you whether that
18 model actually gives you the sensitivity that you
19 want. Will it happen tomorrow? Probably not.

20 So over the period of time, as you develop
21 these critical parameters and then the in vitro
22 release tests that are discriminatory enough in 5

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1 to 10 percent of the time, 5 to 10 percent
2 differences that yields the differences in in vivo,
3 then you come to a conclusion, now my model is
4 there.

5 Then you see whether it will generate the
6 formulation differences, the outcomes you want
7 in vivo. Then you come to a point when you say,
8 okay, now maybe I can believe this in lieu of the
9 bioequivalence testing that Paul is trying to say.

10 But it is coming. My thinking is, this is
11 the same thing as we had when we generated the USP
12 testing for dissolution with the paddle method
13 versus basket. We came all the way through so many
14 ways of doing this. We are generating so many
15 intriguing new testing for in vitro release, the
16 same thing. The modeling will be there.

17 When we first started modeling, probably
18 Dale knows, we hired people, consultants. And then
19 the first thing that the guy said was, "Oh, this is
20 modeling?" And I said, "What is your background?"
21 And he said, "I actually model the traffic in New
22 York City. That's my experience."

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1 What that got to do with anything? Because
2 the modeling is nothing but mathematical equations
3 connected. Right? Modeling is nothing else. It's
4 all mathematical modeling. So mathematical
5 modeling needs the input. The input needs
6 discriminatory testing. And therefore, we come to
7 a point, a certain point, that we will have
8 outcomes that are discriminatory enough that, in
9 lieu of in vivo, we could use it. Thank you.

10 DR. CHOI: Thank you.

11 We will move on to our last priority area,
12 which is on leveraging big data for decisions
13 related to generic drugs. We actually only have
14 about one to two minutes left in this panel
15 session, so I would like to ask Charlie to provide
16 his thoughts on this priority.

17 MR. DiLIBERTI: Okay. I'll be very quick.
18 I think artificial intelligence is really coming of
19 age now, and there's a huge opportunity to use
20 artificial intelligence to examine the FDA review
21 process of ANDAs. I think there could be enormous
22 gains in terms of ensuring consistency and quality

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1 of reviews, as well as facilitating the review
2 process for the reviewers, not to replace the
3 reviewers at all, but to sort of be like the iron
4 man suit on top of Tony Stark, to enhance his
5 capabilities.

6 For example, if you have a new ANDA that
7 comes in with an unusual situation, how do you
8 currently go about figuring out is there a
9 precedent for this; whereas if you had artificial
10 intelligence, it could spit out, okay, here are the
11 17 precedents that are related to this, and here's
12 how we handled it in the past. There's just
13 tremendous opportunity.

14 DR. CHOI: Thank you.

15 DR. GROSSER: It's a lot like traffic in New
16 York City.

17 (Laughter.)

18 DR. CHOI: Thank you so much. We will have
19 to end our --

20 DR. ZHAO: Just one minute. I think we
21 welcome that idea. Actually, there is some
22 unrecognized effort. Within FDA, we are using

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1 machine learning. There is some in the audience,
2 really brilliant. We are trying to use big data to
3 help lots of things. In the future, 20 years,
4 maybe no reviewers will be needed; artificial
5 intelligence does read the review, then organize
6 the data in a way automatically. I'm kidding.

7 DR. CHOI: Thank you. We thank the panel
8 for your valuable comments. And again, if you have
9 additional comments, please submit them to the
10 docket.

11 Now, we will have our office director,
12 Dr. Cook Uhl, provide the closing remarks for this
13 workshop.

14 Closing Remarks – Kathleen Uhl

15 DR. UHL: Good afternoon, everyone. Can you
16 hear me? Okay. Having sat in the audience, I
17 wanted so much all day to say, "Speak up. We can't
18 hear you." So I was glad to hear Stephanie say
19 that this afternoon.

20 I thank the organizers here, and especially
21 ORS, for giving me the opportunity to close this
22 meeting. I want to start first of all with

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1 thanking industry.

2 I thank you guys for being here. I thank
3 you for the input and the dialogue. We are in
4 year 5 of GDUFA I, and we were required under GDUFA
5 to have a public meeting to get input into the
6 regulatory science program. The last four years,
7 we did this via a part 15 hearing. That was less
8 than optimal, and we had specific feedback from
9 industry that requested we do this more as a
10 workshop.

11 So this was an experiment. Everyone in this
12 room understands experiments. This was an
13 experiment to do this as a workshop. And I have to
14 say, early in the day, I was a bit skeptical. I
15 say that because it took this group a little bit of
16 time to warm up. The morning seemed more scripted,
17 and the afternoon seemed much more dynamic and
18 interactive.

19 I thank you guys, especially the last panel,
20 for hanging in there all day and getting us to this
21 point of what a panel and a workshop is about,
22 which is interactive conversations and dialogue to

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1 move the issues. So I thank you guys for that.
2 The other thing is that there's a lot of
3 other people that I need to thank here. I want to
4 express my appreciation to everyone who attended
5 today's workshop. The room was pretty full early
6 in the day. We've had kind of a dilutional factor
7 throughout the day. I don't know how that's looked
8 like on the internet because there were a lot of
9 people attending off site.
10 But I want to thank everyone for taking the
11 time out of your very busy schedules. Many of you
12 flew in from out of town, demonstrating to us the
13 importance of this topic, and we really value your
14 input. So thank you very much for your attendance.
15 I want to thank the speakers and the FDA
16 leads for each of the sessions. You all provided a
17 very informative overview of the regulatory science
18 landscape for generic drugs, and I thank you also
19 for taking time out of your schedules and for
20 making such significant contributions to this
21 workshop.
22 I want to thank the FDA session leads

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1 because this was a bit of stepping out of a comfort
2 zone for some people, so I want to thank them for
3 coordinating the speakers and the panel members in
4 order to construct such engaging sessions. So I
5 think next year, we might have to figure out how to
6 get coffee here early in the morning to get
7 everybody jazzed up rapidly.
8 I also want to thank the panel members. I
9 really appreciated hearing what you had to say, and
10 I think your perspectives on some of these
11 provocative areas were really valuable, as Rob and
12 his group go back, and distill through all these
13 comments, and decide how are we going to best spend
14 a limited budget because there's no shortage of
15 suggestions you guys give us. We usually end up
16 with probably a billion dollars' worth of science,
17 and we have in the low millions. So I thank you
18 guys, the panelists, for all of your input.
19 I also want to take a minute to thank the
20 people who work for Rob, the people in the Office
21 of Regulatory Science. So if anyone's in the room
22 who's in that group, can you just raise your hands?

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1 (Show of hands.)
2 DR. UHL: A huge shout-out, thank you, to
3 all of you guys. It was imperative to have them.
4 (Applause.)
5 DR. UHL: I was scripted to say thank you
6 for volunteering to assist, but I would guarantee
7 you that you were volun-told to assist on this
8 workshop, and I thank you for that.
9 For those of you who are not part of the
10 agency, you probably don't realize that putting
11 together a workshop and putting together a part 15
12 are entirely different. A part 15 hearing is not
13 that difficult to put together, certainly much more
14 challenging to put together a workshop with
15 panelists and such. And so it's a really huge lift
16 to do that.
17 I especially want to thank Lieutenant
18 Commander Murewa Oguntimein.
19 Is Murewa here? I don't see her hair, so
20 I'm sure she must have stepped out.
21 Murewa made the Commission Corps proud.
22 There is no doubt that this workshop would not have

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1 been as productive as it was without Murewa. She
2 did an exceptional job in ensuring that we had all
3 the necessary volunteers. She worked extensively
4 with the room coordination staff here at FDA about
5 securing this room and about coordinating
6 logistics, and a whole lot of work behind the
7 scenes. So great job, Murewa.
8 I also want to thank the OGD communications
9 staff for their support in promoting this workshop
10 both internally and externally. So thank you to
11 Jordana O'Grady and her staff.
12 The regulatory science program is a platform
13 that allows for collaboration between FDA and our
14 external stakeholders to provide tools to
15 efficiently develop and evaluate generic drugs
16 across all different types of drug product
17 categories.
18 FDA and OGD will carefully consider all
19 comments received today as well as submissions to
20 the docket as we develop the fiscal year 2018
21 regulatory science initiatives under GDUFA, and
22 that will then be for GDUFA II. Once approved by

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1 the CDER center director, who is Dr. Janet
2 Woodcock, this priority list will be posted
3 publicly on the GDUFA regulatory science webpage.

4 I want to remind everyone that the docket
5 will remain open until June 2nd. We strongly
6 encourage all interested parties, so those
7 attending in person and those who are by webcast.
8 And you may know others who are interested in this
9 field but were not able to attend, and if that's
10 the case, if you could, please encourage them to
11 submit comments to the docket. That would be
12 really helpful, too.

13 It is this type of input, this external
14 input, that makes this regulatory research program
15 so robust. And you may call this a regulatory
16 science program. I do like kind of a new term
17 that's being used around regulatory science at the
18 agency, which is "decision science." It's the
19 science that typically is not done elsewhere that
20 leads us to be able to make important regulatory
21 decisions, whether those are decisions on
22 advising industry in how to develop products as

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1 well as making internal regulatory decisions.
2 So we really thank everyone again for their
3 participation. And I guess I'm the one who gets to
4 say that today's meeting is concluded. So thank
5 you very much and have a nice evening.

6 (Applause.)
7 (Whereupon, at 4:28 p.m., the meeting was
8 adjourned.)

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