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

May 3, 2017

A Matter of Record
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FOOD AND DRUG ADMINISTRATION

Generic Drug User Fee Amendments of 2012
Regulatory Science Initiatives:

Request for Public Input for
FY 2018 Generic Drug Research

Public Workshop

Wednesday, May 3, 2017
8:33 a.m. to 4:28 p.m.

FDA White Oak Campus
10903 New Hampshire Avenue
Building 31, Room 1503
Silver Spring, Maryland

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:33 a.m.)

Opening Remarks – Robert Lionberger

DR. LIONBERGER: Good morning, everyone. I would like to invite the panelists on our first panel to come up and please take your seats at the panel, and everyone else in the audience to please be seated.

This is the 2017 Generic Drug Research Public Workshop. We welcome both all the attendees in the conference room and those of you viewing through the live webcast. My name is Dr. Robert Lionberger, and I'm the Director of the Office of Research and Standards in the Office of Generic Drugs.

The purpose of this workshop today is to seek input from various stakeholders on research priorities for generic drugs. The workshop is divided into four sessions. For each session, FDA and industry representatives will provide their perspective on regulatory science issues for generic drug research.

There will also be a public comment period in each panel followed by a panel discussion. We'll be taking the information that will be discussed at this meeting and written submissions to the docket in consideration as we develop our 2018 regulatory science plans for generic drugs.

So before we begin the meeting, I'd like to go over a few logistical items. Please silence any mobile devices as they may interfere with other people being able to hear the meeting. If you've not already done so, please check in at the registration desk outside the conference room during one of the breaks. Between each session, we'll be having a 10-minute break while we reset the panelists and speakers and we'll have a one-hour lunch break.

If you'd like to have lunch here during the morning break, please go to the kiosk and order your lunch during the morning break, and then it will be available at lunch, at the lunch break. We have overflow rooms behind this room that are set up with tables for lunch break, so you'll have

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plenty of space here to sit down and have conversations and lunch outside of the hallway. The restrooms are located outside the main entrance, past the registration desk.

The workshop is being recorded and transcribed, and there will be both the video recording, and the transcript will be available on the FDA website after the meeting and after they've been prepared.

Finally, during each panel discussion, there will be a short public comment period, and we encourage people to not interrupt the session during the public comment period. All the requests to make the public comments were made according to the Federal Register notice, and FDA has notified those who will be speaking during the public comment period.

However, during the panel discussion, the moderator or the panelists may ask questions of the speakers from the public comment period, especially if there are any things that they would like to hear more about or follow-up questions. So we ask

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that the speakers from the open public hearing remain in the front row so that they are accessible to the panelists for the public discussion. If you're requested by the moderator to speak, please approach one of the two central microphones in the thing.

So with those logistical details, I just want to give my introduction here again and remind you of the goals of the workshop. It's to communicate what the current status of regulatory science initiatives for generic drugs are. So in each of the panelists, there will be an FDA introduction that will give our perspective on some of the things we've worked on so far and some of the scientific gaps that are remaining. This should help frame the discussion in the panel.

Then we'll be hearing opportunities for industry and the public to provide their input into each panel area, and we've provided opportunities for representatives of the generic industry to participate in each panel, both on the panel and the person making a formal presentation if they

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would like.

If during the course of the meeting you identify other things that you think we should be aware of and you don't have the opportunity to put them into the record at the meeting, please go to the docket mentioned in the Federal Register notice and submit written comments to that docket. I believe it will be open for approximately 30 days following the meeting.

As well, if you go to the Federal Register notice, there is a process for confidential comments. So again, by default, comments to the docket are public, but there is a process outlined by which you can submit comments that may contain confidential information that we would also consider in developing our regulatory science priorities.

So if you've participated in this process in the past few years, I think what you'll notice this year is a very different format. So we're piloting this with the panel format of industry and FDA presentations followed by open discussion.

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One of the reasons is that we're trying to be responsive to some of the comments from the industry on identifying ways that there could be more back-and-forth engagement and discussion about the regulatory science priorities. We've also tried to, from FDA's perspective, outline some of the things that we think we want to do ahead of this meeting so that we can have feedback and discussion around that.

So because this is a new format, you will be receiving a link after the meeting if you signed up to provide some feedback on the format and the balance between presentations and discussion time. So we value that, and we'll use that to optimize the meeting process going forward. So again, it's a new process this year, so we really welcome feedback in terms of making it work better.

As we move into the content of the meeting, as we look back over the past five years, what have been some of the impacts of FDA funded research? When I think about these things, I think really of the three large categories of impact: access to

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generic products in all product categories; building confidence in generic substitution through strong scientific evidence that supports our both standards for approval and quality of approved products; and developing better tools for the development and review of generic drug applications.

This is something that helps both the industry working on developing the products, but also our reviewers evaluating them. So as we advance the underlying science, we can make both the development and review of generic products much more efficient, and that drives a lot of the cost savings that results from generic drugs.

For this meeting, we have strongly focused on the first theme here - identifying access to all product categories. And one way to think of the motivation for this is even with the great success of the generic drug program -- so this is directly from the AAM website and their yearly report on generic drugs, most recent one -- 89 percent of prescriptions dispensed in the United States only

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account for 27 percent of drug spending.

If you do the math on this calculation, you'll see that there's still very large markets without generic competition even though we've reached a high volume of prescriptions. So we want to identify through this workshop what scientific areas can really advance generic competition into all of those markets. We're really focused on that.

So today, throughout the four panels, you'll hear 15 proposed research priorities from FDA which we think can accelerate access to generic drugs. And we've really put these out there to really spur the discussion.

So we welcome discussion around these topics, input, and alternatives. We'll ask each panel, are there things that we haven't considered that should be on our science agenda. But we really tried to focus the topic for this meeting on what are some of the scientific areas where we can accelerate access to generic drugs through either new bioequivalence methods, where there's no

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pathway available, or optimizing existing approaches to make a more efficient approach that works for both product development and product review.

So in my slide deck, I have the list of the priorities that we proposed just for the record, but we'll be discussing them in detail in the individual scientific sessions.

With that, I'd like to introduce Dr. Stephanie Choi, who is the Acting Associate Director for Science in the Office of Research and Standards. She'll be moderating the first session on equivalence of complex products.

I also want to recognize Stephanie. If you've been involved in the logistics of this meeting, you have been directly working with Stephanie. She is really the one that's responsible and deserves all the credit for making this meeting run effectively and well.

So I'd like to really recognize her efforts on this, but also introduce her as the moderator of our first session, so welcome Stephanie.

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DR. CHOI: Thank you, Rob. The first speaker for our session will be Dr. Jeff Jiang, Deputy Director in the Division of Therapeutic Performance at FDA. And he will be giving an FDA research update on complex drug products.

Dr. Jiang, if you can please approach the podium.

Presentation – Xiaohui Jiang

DR. JIANG: Good morning, everyone. Thank you, Stephanie, for the introduction, and welcome to this public workshop. It is my pleasure, honor to start the first session on equivalence of complex generic products.

In the next 15 minutes, I'm going to provide you an overview of our current GDUFA research in this area and show you how we can use characterization and in vitro testing to establish equivalence and help the industry to development of the product as well as for our review to go forward.

So first let's have a common understanding of what is a complex product. I'm showing here a

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baseline of the published GDUFA II commitment letter, complex product due to either active ingredient, complex active ingredients, complex formulations, complex route of delivery, complex dosage form as well as drug device combinations, although some of them, for example dosage form and formulation, might be overlapping.

For this session, as highlighted, we're going to cover most of those categories except the locally-acting drugs, which will be discussed in the next session as well as the drug device combinations.

First, let me start on the active ingredients part. This is related to the drug substance. I will discuss our project in this area, then transition into the project related to the product.

For this particular area, we have external contracts and the grants ongoing, so those things are focused on a more complex system, namely naturally derived products. We hope our collaborators are using orthogonal characterization

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master to elucidate molecular structures as well as their distributions. Furthermore, those characterizations will be tested through some mathematical approach in the research to see how many characterizations are sufficient or needed to establish those equivalents.

We also have internal projects running with various laboratories inside the agency. So those projects are more focused on the immediate regulatory needs, for example on peptide-related analysis and the immunogenicity-related evaluations and also some other areas.

So the outcome in this particular area, we have been publishing product-specific guidances on specific products, and in the past have been working on glatiramer acetate, sevelamers, then - followed on colesevelam, omega-3 related products, and so on.

Another thing on this year's agenda is for the upcoming guidance for highly purified synthetic peptide product, which can reference recombinants with NDA peptides.

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In the next few slides, I will highlight some of our internal research outcomes. So in this particular case is the peptide-related analysis. In the past, we have been using the drug substance to do this kind of practice.

Shown here is using the drug product of salmon calcitonin. As you can see, on the first -- the top chromatograph -- is total iron current. The major peak is the API, but those shoulders, those smaller peaks are peptide-related impurities.

The bottom spectrum is ms/ms spectrum, peaking one of the impurity. And really, you can see from that the sequence of that peptide impurity is elucidated at the bottom. By the way, salmon calcitonin is a surrogate to amino acid peptide.

So in comparison, the LC-MS-based approach is much more sensitive than the standard USP LC-UV approach as you see in those comparisons. I am not going to into the details. So those are the moving-forward standard with the agency on peptide-related product.

The next research project highlighted here

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is in the Office of Biotechnology Products by Dr. Verthelyi using the in vitro approach to mitigate or assess some immunogenicity concerns, particularly here, you see, using a cell-based assay to detect inner immune response and modulate impurities. We envision this kind of approach can be used in a comparative study for complex generic products.

Now, let me transition into complex formulations at the product level. So here, I'm showing you some examples of what I'm talking about. So I will not go into details for each of those products, but at least you can see how differently those products are.

The first thing again is characterization. So we want to use advanced analytics to understand the product attributes as well as those important functional excipients, as well as in addition to develop our analytical method to detect those complex products in the blood, urine, or wherever we can detect them to facilitate the bioequivalence development.

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Particularly showing an example here, it's related to the functional excipient in PLGA products. This is our collaborators' work, using C-13 NMR, not only to be able to look in at the details of lactate-co-glycolate, but as well as their ending group.

So based on those research outcomes, we updated our product-specific guidance for the products in this area. So not only do we need to look for the Q1/Q2 aspect, we also need to look into the details of those functional excipients.

This is another example. This is a study on generic sodium ferric gluconate. We have a research contract ongoing with an outside collaborator as well as an inside collaborator at DARS, looking at the bioanalysis and the clinical BE study designs. But in addition to that, we also performed characterization on the drug product because the iron colloid-related product as well is an important area for us to understand. So shown here is a different orthogonal characterization method we employed to study the particle size

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distribution. So that's the continuous. We really try different methods to understand what's going on with this class of drugs.

Now let me switch gears to talk about another aspect of product characterization to understand the manufacturing and formulation processes on the end product's quality attributes. Most of those products, as we understand, are sort of required by regulation to be Q1/Q2 to the reference product. However, there's still quite freedom space in that, depending on the manufacturing process impact on the performance of the drug.

So this example shown here is a collaboration with the University of Connecticut in Dr. Burgess' lab for risperidone-related products. She developed different formulations using a different approach. As you can see, they themselves are Q1/ Q2 to each other, but however, the characteristics as well as some performance are quite different.

So now the final part I'm going to talk

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about is in vitro release testing. Traditionally, in vitro release testing has been used as a quality control method, so one of the things is to cover different products.

As you can see, ophthalmic suspension/ointments, periodontal, and parenteral, and so on and so forth, as well as different technologies, here some post-release testing methods, USP recommended or FDA recommended, are still quite large and still don't have a recommended method.

Furthermore, we want to see if those methods can be further utilized in an in vitro/in vivo correlation manner. And at a certain point with specific products, it maybe can be substituted as a bioequivalence method.

So due to the time constraint, in the following slide, I will not go into the details of the research outcome -- the research details -- but I will highlight those projects so that you can see the different areas we are undertaking.

This one is ophthalmic drug release.

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Ophthalmic drugs are very different, working on the eye. And we want to develop testing that mimics eye viscosity and the flow rate. On the right, we also developed suspension drug products, IVIVC model, in our collaborator's lab.

This is showing the microsphere-related product at the University of Michigan. Our collaborator developed a so-called cage model. This model can mimic -- have no impact due to the model itself -- in vitro and in vivo and also will be able to establish some kind of IVIVC.

The importance of this model is it gives the developer an opportunity to take those microspheres out so that to study how these things impact on the performance.

The last example is related to the progress at the University of Connecticut, working on those formulations. This one is showing really beyond the in vitro release. Also, Dr. Burgess has conducted a study using the in vivo animals, and deconvoluted the profile, and established a very nice IVIVC correlation. So with this process, she

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also tested different releasing methods to see how discriminant those things are.

So in summary, what I want to point out is advanced analytics is really a cornerstone for the development in this area. For the drug substance, definitely it is necessary to use those techniques to establish the equivalence of active ingredients.

Further, for the product, you can capture those critical quality attributes for the equivalence. On the other hand, in vitro testing complements the characterization. It can use a biological test to further confirm identity and the function of the active, as well as measure the performance of the proposed drug product. The in vitro release testing is very promising not only as a quality control method but can step into the bioequivalence paradigm when it is ready.

For the panel as well, we hope the discussion will be focusing on four areas. Number one, again, it's on the characterization and using advanced analytics to elucidate chemical composition, molecular structure, as well as the

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distribution of active ingredients.

The second part is to mitigate certain risks, particularly immunogenicity with a peptide-related product and how we can use in silico, in vitro, and animal studies to reduce such risk.

The other two are related to the drug product. One is on the characterization of the product, again, from different angles, looking at particle size, shape, surface characterizations, and many other things to fully characterize the properties of a complex drug product.

The last one is how the in vitro BE method can be used. Particularly, we point out the long-acting injectables include suspension as well as microspheres to see which kind of research or advance can help the industry.

So without further ado, let me stop here to introduce the next speaker.

DR. CHOI: Thank you. Our next speaker is Dr. Robert Bellantone from Physical Pharmaceutica, and he will be giving an industry perspective on generic drug research needs.

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Presentation – Robert Bellantone

DR. BELLANTONE: Thank you. Good morning. This is kind of strange territory for me. I've never really said anything of note in my whole life in 10 minutes or less except when I say no to my kids when they ask for exorbitant amounts of money, but we'll muddle through and see if we account make it through here.

Today we're going to be talking about cyclosporine ophthalmic emulsion, and I'm going to sort of jump to the end. I have a lot of material in the slides. I'm not going to really parallel the slides too much. This is more in the flavor of notes that you might take. So I'm going to talk about what's in the slides, but I'm not going to mimic the order or the detail. This is more supportive detail.

So with any ophthalmic emulsion, when you administer, as we know, in the eye, it's got a very short residence time. You blink, half the formulation is instantly gone, and so on, and so forth. So what will happen when you're doing that

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is a lot of the formulation goes away. But it is a liquid with a viscosity with a surface tension, and so what will be left behind will be a thin film. That thin film is typically on the order of, say, 50 microns in thickness.

So this has some profound effects, so I want to talk about that. I also want to talk about what we really can't know about the structure of the globule. So just knowing the particle size will not tell us things about the drug distribution within the globule. And those are the two things that I'm going to focus on, the thin film aspect, and the unknowns in the globule, and how they will carry forward, and how they should be reflected in an in vitro release rate test.

We all know that, if you want to do an IVRT for an ophthalmic emulsion or an ophthalmic product, you have a time constraint. There's a short residence time in the eye. But the physical chemistry of the situation also affects and puts time constraints on what you're looking at.

This again gets back to the fact that you

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have a very thin film that survives the initial blinking. It will get diluted and removed with tears, but you still have processes that go on in the time frame when it's still sitting around.

So the two processes that are of main concern in no particular order is, first, because the film is very thin, there's an enormously rapid temperature response. You have a drop, say, of room temperature, 20 degrees C. You administer it to the eye. It comes up -- simple calculation, comes up to the ocular surface temperature or thereabouts in about a second. So you have a rapid temperature distribution.

For cyclosporine, that's particularly interesting because cyclosporine, as the temperature goes up, as you would expect, the solubility in the oil goes up, but the solubility in water actually goes down. And this is published data, and we have done determinations and confirmed that.

So that is one of the things that goes on, is you have an extremely rapid temperature

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response. The other thing that's associated with the thin film is there's not a lot of drug in a thin film. You have an enormous surface area, but you have a very small, shallow drug depot.

So what happens is, as the drug is being absorbed or removed, you're going to deplete what it's in the aqueous phase very rapidly. That's typically 5 or 10 percent with the cosolvent effects and so on that we measure.

Then what will happen is after you deplete that initial 5 or 10 percent, because of the thin film effect, now you're starting to expose the redistribution of the drug out of the globules into the aqueous phase where they can subsequently be released. And that will actually come in two phases, and I'll show you some data in a minute.

Some of the drug gets out of the globules rapidly, and some of the drug that's in the more oil-rich portions of the globule get out of the globule more slowly, and that will limit the release.

So those two effects are very important.

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The third effect that I want to talk about is with regard to the globule itself. The globules are small, and we like to talk about the distribution in the aqueous phase, the surfactant phase, the oil phase, but there's a problem with that.

If you assume no miscibility and you calculate the thickness of the surfactant layer, you would come up with something around 10 or 20 nanometers, which coincidentally is around 10 or 20 molecules between in thickness. But because of the high miscibility between tween and the oil, that is really not the structure that you have. You have kind of a transition layer.

So what I've done in the left-hand panel is I've shown the idealized non-miscible calculation. And I've attempted to show on the right-hand side, for better or for worse, that you have this thin 10- or 20-nanometer maybe transition zone, where you have the tween and the oil and water mixed in unknown proportions. And they are going to be process-dependent, we think, because it's not self-emulsifying. So it's not an equilibrium situation.

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It may not always go to the same place.

Because of that, you don't know the structure inside the globule. You don't know the distribution of the drug inside the globule, what's in the oil-rich versus surfactant phase, and this affects your release. And the takeaway for that of course is just knowing that globule size is not sufficient to predict the release characteristics.

One approach that we like to think of is if two formulations are going to behave equivalently, number one, they should start out at the same place. And number two, when introduced into the eye with the rapid temperature change and the depletion of the drug due to release and absorption, they should respond in the same way.

Well, in terms of your testing, your parameters to measure, such as globule size and so on, are going to reflect the state of the drug product before you introduce it. The response, which is going to be a function of time, is going to be your release test.

So I'm going to skip over this slide. This

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is more of an information slide. I said a lot of that already. So let's look at some data that we have generated in our labs. We have technology that was referred to earlier, PMD or pulsatile microdialysis. And this particular technology uses very small geometry set-ups.

So the radius of these probes that we use are tubular probes, and we released a drug from them. It's about 100 microns. So you get the rapid temperature jump when exposed to a receiver fluid at a temperature that is different from the storage temperature, and you get rapid release.

As we can see from the data here, all of these profiles show basically two phases at early times, say, in the first two minutes -- and we can get that data because of the size of the probes being very small.

In the first two minutes, you get a rapid release. Now, we think that the first 5 or 10 percent comes from the drug in the aqueous phase. Maybe the next 5, 10, 15 percent is drug that is petitioning out of the globules readily

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into the aqueous phase and can be released. And then at later times, 5, 10 minutes on, you get a much slower release. This is reflective of the drug having a slower partitioning out of the more oil-rich phase of the globule into the aqueous phase, and then it can be subsequently released.

This is why, when I was looking earlier at the lack of the structure, the clean structure of the surfactant layer, you can't predict that ahead of time. You can only get the effects of all of these things together, the temperature, the depot or lack of, and the redistribution through your release test.

So what we did in this slide, the left-hand panel reflects a particular Q1/Q2 formulation, and in that formulation, we released into 20 degrees receiver. It was stored at 20 degrees going in. So there's no temperature effect. This is just the depletion effect, okay, and the redistribution.

The higher, the empty squares, the higher plot, is the release into 35-degree medium, and that separates out -- or that's the effect of both

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depoting or lack of depoting and the sudden jump in temperature.

Now, if you look at the right-hand plots, in the right-hand panel, these are two formulations, both Q1/Q2, but manufactured by different processes, both stored at 20, both releasing to a 35-degree medium. And what you see is there are effects of the processing. But with all of these, again, you see the biphasic release.

With all of these, because the geometry is similar to what's in the eye and the conditions are similar to what the thin film is exposed to in the eye, we're able to get this data at early times, and that is critical. And that has very little to do with the residence time and a lot to do with the physical chemistry and fluid dynamics of what's going on with the formulation.

So we think that's a really good test. And we think that any test should reflect the ability to redistribute, the ability to mimic the temperature changes, and so on. If you don't have those, we don't think it's a good test because

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you're not looking at the right circumstances that govern whether two formulations are equivalent in their behavior in vivo.

I just want to make a comment because I've been on record as being critical of using Franz cell tests for this. And the Franz cell gives you none of those, so I'm going to move on to the last slide. But you can read about how Franz cells do not allow you to do that.

So in summary, those are the takeaways. We feel that we've described an appropriate test, and with that, I'll say thank you very much to the FDA. And also, I would like to thank you all for listening. And thanks to Piyush Patel and Kosha Shah, two scientists who have helped me drive the bus on this project.

Thank you.

(Applause.)

DR. CHOI: The next speaker is Mr. Vincent Andolina from AuroMedics Pharma, and he will be giving us the second industry perspective on generic drug research needs.

Presentation – Vincent Andolina

DR. ANDOLINA: Good morning, and thanks, everyone. I won't focus on the science, but more the regulatory since this was the only iron colloid product with an AB rating. So my interest is how that happened and how there have been none since.

Next is my disclaimer. These are only my opinions, and I'm not trying to disclose any confidential or trade secret information.

As Dr. Jiang spoke, establishing sameness, it's difficult if the RLD is not completely characterized as heterogenous or otherwise variable. And if it's patented, how do you show sameness without infringing? There is some differences permitted, for example impurities profile. However, if the impurities are suspected of immunogenicity, that causes further study.

Representative iron colloid products are polymers of variable molecular weight: iron dextran the first; sodium ferric gluconate in sucrose; iron sucrose, which is Venofer; ferumoxytol; and ferric carboxymaltose.

Iron dextran was the first, and the labeling contains a boxed warning of the risk of anaphylaxis. There are two products marketed and approved that differ in molecular weight and are BP rated, not substitutable.

The next is the compound of interest for this presentation, sodium ferric gluconate complex in sucrose. The RLD is Ferrlecit. The generic was approved based on bioequivalence and extensive physicochemical characterization studies.

Iron sucrose is probably the market leader, or it was back then. It is Venofer. Ferumoxytol is a newer variant. Ferric carboxymaltose is from Luitpold, who markets Venofer.

Now, the actual submission. Sodium ferric gluconate was developed by a virtual company, GeneraMedix. All lab work was performed by contractors or partners. The initial information transfer from FDA was done by telephone, which would not happen today. We were told that, if it was Q1/Q2, physicochemical characterization, and if the drug product could be shown to be a solution, a

thermodynamic equilibrium, we thought it would be eligible for a biowaiver.

We proceeded to have the product developed. No bioequivalent study was conducted. We manufactured an exhibit batch according to the requirements of the time and got our Refuse-to-Receive. Again, I want to point out the path forward was discussed via teleconference, which would not happen today.

Our first substantive review by a chemist resulted in a major deficiency. The chemist is part of today's panel. Again, the path forward was explained to us by the chemistry team leader and the review chemist by phone informally, which was immensely helpful in actually getting the product approved and in agreeing on a path forward.

Our request for a waiver of bioequivalence was ultimately rejected, and we were asked to do a bioequivalence study along the lines of a bioavailability study that was done on behalf of the reference product using a compartmental model.

Let me just say a couple of words about

that. Iron is conserved by the body. Injectable iron, colloids, you cannot inject ferric chloride. It's toxic. That could not be injected. And furthermore, labile iron or free iron is considered to be the impurity of -- you might call it -- of most interest for toxicity.

The original bioavailability study that was published used a compartmental model. Injected iron is taken up by the reticuloendothelial system and then sent back into the body in the form of transferrin- bound iron, which is obviously not toxic.

We had a bioequivalence study performed with a relatively small sample size and a crossover design. Ultimately, that bioequivalence study was rejected, again with extensive communications with the Division of Bioequivalence.

We went forward with a parallel bioequivalence study using conventional data analysis. That was also informally reviewed by the Division of Bioequivalence, again something that would not happen today, I can assure you. The

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second study was conducted, submitted, and accepted in 2009. Actually, just to see how fast the time was, dosing was in June. We submitted the study in September. We got an acceptance by the bioequivalence division in November.

As of September 2010, the ANDA was approvable as far as OGD was concerned. It was waiting for a citizen petition to be responded to. That was done on March 31, 2011, at which time the ANDA was approved. There is a draft guidance on SFG, as we call it, published. It gives the bioequivalence parameters and the physicochemical characterization parameters.

I would say the paradigm of FDA doing research and telling industry what they should do at an arm's length is difficult because industry doesn't know what they need to do, what results will be approvable, and so on.

To get more feedback is difficult today. You can submit a control correspondence. That has limitations. Any other kind of feedback, you can ask for a meeting. That also doesn't work that

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well now. In my recent experience requesting a meeting, it takes about a month to see if the meeting will be granted, and it must be scheduled or you're told that it'll be done by e-mail. Again, if it's by e-mail or on paper, there's no back and forth. There's no opportunity to reach a consensus on the path forward.

So that's my little soapbox speech for the day, and thanks, everyone.

(Applause.)

DR. CHOI: The last speaker for the session is Dr. Russ Rackley from Mylan Pharmaceuticals, and he will be giving us the third industry perspective on generic drug research needs.

Presentation – Russell Rackley

DR. RACKLEY: Thank you for the opportunity to present this afternoon. Again, I want to speak to the challenges of demonstrating statistical non-inferiority for irritation transdermal drug delivery systems using the OGD guidance. Just to comment, this reflects my views, not the official opinion or policy of Mylan.

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So the problem previously with adhesion and still currently with irritation is that using the OGD's method for good-performing products, irritation scores approach zero. And thus, the non-inferiority margin is proportional to the mean score for the reference.

The consequence of that is the non-inferiority margin essentially approaches zero. This makes this requirement practically one of demonstrating superiority to a good product and may require extraordinary powering requirements.

So thus, it's believed that the current guidance, although not intended to do so, effectively serves as an inappropriate block to generic approvals.

Let's take a look at the statistical metric. It's based on the upper 95 percent confidence interval of the mean test score minus 1.25 times the mean reference, which must be shown to be less than zero. This equation can be rearranged to demonstrate the reference mean score is a denominator. And as you know, as denominators

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approach zero, this could be problematic for inflating the metric and meeting this criteria.

I tried to illustrate this a little more graphically here. The line of identity here is the blue line, which reflects equivalent scores for test and reference products. The evenly dashed line here is the current irritation guidance margin for non-inferiority. And I've shown the uneven dashed line as for comparison for the adhesion, a non-inferiority margin.

I will comment that I think with the new adhesion guidance, this is an improvement that solves a problem partially, but still seems to be somewhat rigid. So this orange area seems to be an area qualitatively you can say forces a test product to perform in a somewhat more superior manner than necessarily demonstrating non-inferiority.

So again, on the adhesion metric, this just compares the old metric and the current irritation metric to the current adhesion metric, which is the mean of the test minus the mean of the reference as

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the upper 95 percent confidence interval, which is less than or equal to 0.125.

Again, I think this seems to be still a fairly rigid criteria, still working and understanding how well that works. Perhaps it could be overly conservative, but I'd request maybe that we better understand the rationale for the 0.15 criteria.

I thought I would give a couple of examples here to show how the current irritation metric works. This is a study with 36 subjects who were evaluated in a 21-day same-site irritation application of a transdermal drug system patch. It was applied daily for 21 days. And you'll see that the trends here are that the scores on a potential scale of 0 to 10 are around 1 to 2 and maybe tailing off past that for both test and reference.

To better illustrate that with this histogram, you see fairly similar behavior of the cumulative irritation over 21 days. So these seem to be fairly comparable in performance.

When the metric is applied in this case,

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you'll see that the mean test and reference test scores are around 2, so the parameter test minus 1.25 reference gives an upper 95 percent confidence interval less than zero. So in conclusion, this particular case, the product passed with this kind of cumulative irritation.

In a second example, we had a 78-subject study evaluated 21 days of a cumulative irritation, again transdermal drug delivery system, comparisons that were twice-weekly patches. So there are 6 applications over the 21 days. And you'll see the trends here that the scores largely remain around zero.

Illustrated as a histogram, again, you see fairly comparable performance from both test and reference for these products, which largely are centered on zero, indicating no irritation. The current metric applied to this data, you'll see the means are very close to zero, 0.113 for the test, 0.088 for reference. So the end result of this upper 95 percent confidence interval for the current metric is slightly above zero, so the

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product would fail on that case.

So the current guidance suffers from the use of non-linear discrete scale, particularly for irritation results and datasets consisting largely of zeros. As a result, as the reference mean score approaches zero, the non-inferiority margin essentially disappears, which has the effect of forcing a generic to perform in a superior manner or could require powering with an extraordinary high numbers of subjects.

So we feel there's a need for an updated non-inferiority testing method and understanding the current method for adhesion in the modification on the irritation method, so that we can span the spectrum of reference performance, particularly for well-performance reference products, that predominantly score as zeros on both cases.

I'd just reflect just one situation. This has been well-known I think for some time. There was a submission by Teva for a testosterone gel. I think it was originally submitted as a generic product, so the test aligned with that kind of a

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program. However, they ran into this similar problem, apparently with respect to scoring zeros, according to the irritation scale, and suggested this “+1” approach to solve this particular issue.

The filing was eventually converted to a 505(b)(2), and it was eventually approved on the basis of showing neither cumulative irritation or sensitization reaction occurring to study subjects. But the “+1” method proposed basically takes the OGD method and adds 1 to all possible scores.

If we took this scale modified and applied it to the second zero that I showed you that failed, you'd have means that come out right around 1 because that's the lowest score you can get. And the metric then shows the 95 percent confidence interval slightly below zero. In this case, it would pass.

So the issue continues as a regulatory science issue, and we urge the FDA to address it in the coming year as a priority since the effect of inhibiting generic competition for well-performing products is counter-intuitive to public health

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

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

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

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

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complex products are identified, the group is committed to further these discussions in other meetings next week in Basel during the CLINAM conference and the Pharmaceutical Sciences world conference in Stockholm.

So I encourage all stakeholders to participate in these discussions so we can make sure that products developed are of high quality and high safety. Thank you very much.

(Applause.)

DR. CHOI: The second speaker is Dr. Amy Barton Pai from the University of Michigan.

DR. PAI: Good morning. What I'd like to do today is essentially discuss how we can leverage global experience with iron sucrose generics to potentially augment bioequivalence evaluation in the U.S.

Iron sucrose is a smaller molecular weight compound. It's widely used, and it is the most commonly used product in dialysis patients. More than 30 percent of U.S. dialysis patients receive almost 5 grams of elemental iron annually. This is

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in comparison to the average healthy person that absorbs about 1 to 2 milligrams. So while the dosing of iron and amount we give is controversial and beyond the scope of this presentation, I think what it does is underscore that we need safe products.

Many iron sucrose similars are available in Europe, Asia, and South America, and switches are often mandated. The emerging published data on these products across the translational research continuum has been emerging and I think gives us an interesting framework that really does implicate labile iron as being associated with adverse effects.

Animal data has clearly shown that these iron sucrose similars are referred to as such because, ultimately, the challenges we're discussing today and the challenge in creating an exact copy has been shown to increase oxidative stress.

Across a more translational spectrum from cell to animal to human, again we have shown

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repeatedly that iron sucrose similars in comparison to control or RLD increase oxidative stress and potentially vascular damage.

Then ultimately, we are seeing clinical outcomes data, which are showing increased adverse effects that are typically associated with labile iron such as hypotension, reactions with infusion, and lot-to-lot variations.

These are data from a U01 that was recently funded. Essentially, we strived to identify the optimal labile iron assay, which was an HPLC-based assay with a deferoxamine chelation method.

Here what we show is the in vitro labile iron release profile in saline and in serum, and then also in vitro in a rat model. Ultimately, when we're looking at this only-approved U.S. generic, which is sodium ferric gluconate complex, what we've shown is there is no statistically significant difference in labile iron, although we can see some observation that Ferrlecit, for example, has more variability in vivo and is higher in vitro.

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So just to tee this up, we believe that labile iron release profiling is a pragmatic approach to augment physicochemical characterization. We believe there are inherent PCC challenges that are widely observed in this group certainly. We think labile iron profiles are informative to confirm that no significant difference exists in the rate and extent of labile iron, and it supports other in vitro dissolution techniques.

So ultimately, we believe bioequivalence as expressed here is uniquely challenging, and we believe labile iron profiling would be a significant addition to bioequivalence evaluation. Thank you.

(Applause.)

DR. CHOI: The next speaker is Dr. Kenneth Morris from Long Island University and also representing NIPTE.

DR. MORRIS: Thanks, everybody. As said, I'm from Long Island University. And for those of you who don't know, I'm from the Brooklyn campus,

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

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

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

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

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

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

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

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

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

(Applause.)

Panel Discussion

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

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

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

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

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

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

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

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

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

DR. SRINIVASAN: Aloka Srinivasan, vice

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president, Lupin Pharmaceuticals.

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

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

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

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

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

ingredients.
Elucidating the chemical composition, molecular structure, and distribution of complex APIs can present a number of characterization challenges. And I'd like to ask Dr. Andre Raw to start off this panel discussion by commenting on the current scientific gaps and regulatory challenges for establishing active ingredient sameness for complex APIs.
DR. RAW: In the recent history, we have approved complex APIs that are highly heterogenous active ingredients. And if you really think about it, the way that we distilled it was based upon considerations of obviously the molecular structures and their physicochemical characteristics, but other properties, including the sourcing of the material, whether it's synthetically sourced, or whether it's completely synthetically derived, or whether it's a combination of the two, naturally sourced or synthetically derived such as Lovenox, such as low molecular-weight heparin.

Based upon these three attributes, we actually were able to develop criteria that informed the approval of enoxaparin, iron colloids, glatiramer acetate, and the current guidance says we have for Premarin as well as sevelamer.
So these are definite doable problems. We account definitely address these issues. However, I think the challenges that we have is that each API is unique, and for each API, we have to develop tailored criteria -- equivalence criteria -- to address based upon the structures, its sourcing, and biological chemical characteristics to address this. And this does present challenges for scientific as well as regulatory that both FDA and industry have to -- it's sort of a learning curve to address these things. But that's my comment.
DR. SRINIVASAN: Incredibly interesting presentation. And Vincent, thank you for bringing back memories about the iron -- and I do think that FDA has made incredible strides in the area of complex generics, but every complex generic is complex in its own way. Like Tolstoy said, every

unhappy family is unhappy in its own way. Every happy family is the same.
So it's the same way here. What I think industry is looking at is we do not want a changing target. The problem with the generic industry is it has to move very fast. I mean, there are 15 companies who are doing it. I think it's good to come out and talk about it. It's highly competitive. It's also working on a shoestring budget.
So what we are expecting from FDA on this is also guidance and, in some cases, probably the minimum criteria, because there is a destination, and you can reach it in a red 2017 Ferrari or a 2010 Honda Civic. Now, the question is -- both are going to take you there -- I mean, I know it's cool to reach that in the Ferrari, but can I use the Honda Civic?
I'm sorry for that. I couldn't think of anything else. But the question is to come to a point and understand what is enough. And there may be points where it's not enough. And at that

point, go and say, you know what? We are not comfortable. I think we need a clinical endpoint study here.
That's also acceptable. What the industry is looking for is some kind of consistency. Recently, there are rare experiences with products like teriparatide and liraglutide, et cetera, which are rDNA origin.
We all know. I mean, some of us from FDA OGD knew that probably it would be tough to go without rDNA, but there wasn't a very clear directive there, which put people into a little bit of problem. And we would hope -- I mean, these are great, and we want to work with FDA on this, but we would want them to be consistent in their advice.
DR. ROSENBERG: This is clearly a critical priority. And I think one thing that is of great importance is, when you identify perhaps new species, new molecular structures, how are you going to determine what is a critical attribute and what is a non-critical attribute? Because that to me is the next absolutely most important step

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because that will determine essentially what you have to focus on. And if you can't decide if it's a critical attribute or not, then you're uncertain, and how should you manage that kind of uncertainty?

We've published papers on managing uncertainty regarding this kind of issue, but I would turn it back to Andre and say, you identify new attributes. How are you going to determine if they're critical?

DR. RAW: Yes. So one thing that is alluded to is we have new attributes, like for example an impurity. Okay? And the question is, can we develop -- how do I say?

One of the things that is a challenge is immunogenicity, for example. And how can we address models, that are potentially in vitro models or animal models, that potentially could address these to resolve these uncertainties that we have?

DR. KEIRE: Yes. I think some of the models that Daniela Verthelyi in your group is working on are examples of that, the cell-based models, innate

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immunity that can be used to screen these things, once you identify them with the advanced analytics. Right?

I think the paradigm has shifted where before you didn't know they were there. And even if you could know they were there, you didn't know what they were. Right? You just had these little peaks. You could maybe get a mask if you couldn't identify them.

But now the technology has changed. It's a good time to be an analytical chemist, maybe not a good time to be a regulator because all these new things are coming. So one approach could be you could look about what's safe and effective in the marketplace right now. What's in those products that we didn't know was in there before. And at least that's a starting point for some risk assessment. So I think that's the process we're thinking about.

DR. ROSENBERG: Yes. I don't think we should focus strictly on immunogenicity, although that's very important. But there may be other

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attributes that impact other aspects of behavior.

DR. CHOI: Dr. Burgess?

DR. BURGESS: Yes. I just wanted to mention an example from recent work in my lab with OGD, where we've been looking at polymers, particularly PLGA. And we found that very subtle differences in the polymer that you wouldn't have expected have had significant effects on drug release in vitro at least, and we're now studying that in vivo. And this could impact a burst-release in vivo that could affect the efficacy as well as the toxicity.

These kind of changes I'm looking at are with polymers that are purportedly equivalent in molecular weight, in copolymer ratio and n group, but still subtle differences that may be associated with different manufacturing from different sources of manufacturers and could result in, for example, different blockiness or something like that within the copolymers.

Those subtle differences may impact on some types of products and may not impact in other products. And this is something that we think is

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important to investigate because of the potential for safety and efficacy.

DR. SRINIVASAN: That's so interesting, and that probably brings to another topic about the timing because industry has started working on this probably in 2013-14, if not before, on these complex injectables, to bring them to FDA.

I think there seems to be a lag, but FDA has started the work now. Most of them are quite advanced in their research, and it would have been so helpful to have a little earlier advice from FDA on that. And that's also for the future generics, something to be considered, that work usually starts five years before for these products.

DR. CONNER: I just want to readdress what has been talked about, that generic drugs in the U.S., in our system, depend upon an inherent assumption that the drug substance is the same when you compare them.

So we take for granted these days that simple small molecules are very easy to characterize. We don't have any worries that

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they're the same thing. Impurity profile is a different story, but at least we know that the drug substance is the same.

If you went back 30 or 35 years, that wasn't true. Even simple molecules were sometimes very hard to characterize analytically. And advancements in science bring us to a point today where we almost take that for granted. Simple molecules can be fully characterized. We know what they are, and we know when they're the same and we know when they're not.

So I think that the advances for more complex situations, the advances in analytical chemistry is critical. And someday, I'm sure we'll be sitting in a meeting like this, all taking for granted that even these very complex molecules can be fully characterized. But that will be based on the advancement of technology, of which meetings like this, the FDA research program, and industry and academic research programs, will all lead to that.

I also hear two levels -- I've heard two

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levels of complaining in a certain area, one that things move too slowly. I've been here for a while and people were saying, this is a complicated product, and the FDA's not giving us guidance. The science just wasn't there. I mean, in a lot of cases, we don't know.

As science advances -- and it's almost snowballing now due to all these programs -- we get advancements in the areas we need more and more quickly. So when you perceive changes in guidances and changes in thinking both on the industry side and the FDA side, that's due to we have now new information and better, or worse from some points of view -- we're getting it faster and faster.

The FDA is now very good at taking information, kind of mulling it over very quickly, and bringing it out to the public in a guidance, and we're getting better and better and faster and faster at that. So some see that as a disadvantage, but I really see it as an advantage.

I mean, if you're in business, and you're on a clock, and you're on a schedule, that may come at

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a very inopportune time for you. But it's the advancement of science. It's the advancement of regulatory knowledge. And with all these research efforts, it's going to get faster and faster, we hope. And someday, we'll all be taking this for granted.

DR. CHOI: Thank you. I'd like to move to the next proposed priority area. For generic peptide drugs, potential immunogenicity concerns may be caused by variations in the API and/or the impurity profile.

I'd like to ask Dr. Amy Rosenberg to start off by commenting on available predictive in silico, in vitro, and animal studies to evaluate immunogenicity risks due to impurity or formulation differences and any scientific gaps that will need to be addressed.

DR. ROSENBERG: So it's a very interesting area in terms of the word "predictive." So typically, in silico type methods are used in respect of the sequence variations and how those might impact binding to HLA, for instance, and the

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consequences thereof. So that's typically how in silico is used.

In vitro, on the other hand, is something -- and animal studies, are both critically important in evaluating immunogenicity risk of these kinds of formulation and impurity differences.

So I think of this as sort of in a tiered way that you have in vitro studies. You start with in vitro studies that may be meaningful in terms of predicting immune activation. So what are some of those? Cytokine release, perhaps gene expression, and we certainly can think about using next-generation sequencing to look at that rather than the studies and technologies that are more variable.

Particularly important, I think, with these kinds of evaluations are also the animal studies. This is mentioned here. So, in vitro, yes, you can do the kind of studies that we just talked about, where you'd get cell lines that express various receptors for impurities, and you'd use those. And

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that's a good start. You have the use of cell lines or actually human PBL, which again is a bit more variable, but will give you a potential read-out in terms of differences here. And that's what we're really interested in, differences between the generic and the RLD.

But, the ultimate test actually would be animal studies. You can use the inbred strains of mice. You can test the RLD versus the generic, and you can look at parameters of immune responses that are potentially important.

So not just do they make an antibody response, but how quickly do they make an antibody response? What kind of antibody response do they make? What's the antibody isotype? Do you get isotype switching? What's the duration? How long does the response last? And so, you know, lastly, does it have hypersensitivity elements to it?

So you can look at many aspects of an immune response. Do you develop neutralizing antibodies? There are many, many aspects of an immune response you could look at in these inbred strains of mice

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comparing one to another. So, I think that is probably, you know, it is not what people want to go to. We'd like to keep things out of animals. But, nonetheless, I think that can be an amazingly useful tool in addition to the in vitro kinds of studies that we talked about and that Dr. Verthelyi has developed.

DR. STRAUSS: David Strauss, the Division of Applied Regulatory Science at FDA. So, I'll start out saying I'm not an immunologist, but we do have some very smart ones in the division. And, but we know that immunogenicity is very important. It can alter the pharmacokinetics in the assays that are used, the ligand-binding assays to determine pharmacokinetics. And it can also alter the pharmacodynamics of drugs. This can have a clinical impact potentially if it's interfering with the drug-binding target.

And, I think, going forward, we need to know which types of impurities can cause immunogenicity concerns, and there are different ways we could do this, as we've heard, combining in vitro cell

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assays and then moving to in vivo models. We have an effort in our division with human eyes, mouse models that combine a human immune system into the mice and have efforts to use this with large-molecule biosimilar drugs. And this can be expanded to generic peptide drugs as a model that could potentially be used.

And, yes, I think there are opportunities to really translate between in vitro, in vivo, and in silico to understand where the problems can be, and then where needed, evaluate specific drug products.

DR. ROSENBERG: I would just add to that, that we're well-schooled in the quality attributes that contribute to immunogenicity. And those have been published in guidance, our immunogenicity assessment for therapeutic protein products and our article on scientific considerations for generic synthetic salmon calcitonin products.

These are well known, aggregation, the extent of aggregation, the size, et cetera, molecular weights, the deamidation, which we know

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facilitates aggregation, oxidation. We're very well-schooled in the kinds of product degradation or post-translational modifications that contribute to immunogenicity. And those really should be those easily measured and the equivalence of those shown.

I think particularly important are forced degradation studies. So, you know, the generics should degrade in the same way and the same tempo under the same conditions as the RLD. And I think those studies are critically important for being able to look at the propensity of each product to degrade in a way that would potentially impact immunogenicity.

DR. CHOI: Thank you. I'd like to go on to the next proposed priority area, which relates to predictive in vitro bioequivalence methods for long-acting injectables.

If Dr. Diane Burgess could start off this discussion by commenting on when an in vitro/ in vivo correlation would be necessary for an in vitro bioequivalence determination for long-

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

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

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

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

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typically, you're trying to model the human gluteus maximus, so there are differences there. There are differences in vascularity and movement.

Typically, we found that this speeds up release quite significantly in comparing the rabbit model to data that's available in humans for different drug products such as some of the microsphere products like Risperdal Consta.

But it is a good model, and you can get a lot of good information from that. And doing a kind of serial sacrifice and looking at the site can give you really a lot of information. Even the technique of injection of some of these products, the suspensions, but also some of the in situ forming gels and so on, like how you inject into that muscular space, can eventually affect your release profile, and so on. So there is an awful lot to be gained from the animal models.

DR. VAITHIYALINGAM: Okay. Understood. So, it is just not the in vitro, but you have to couple that with some level of animal studies and clinical studies.

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DR. BURGESS: Then you can go back and better design your in vitro model.

DR. VAITHIYALINGAM: Got it. Thank you.

DR. VELAGAPUDI: I have one comment. This is Raja from Sandoz. The animal models, when we do that, like we held monthly injections, and then three-month injections, six-month injections, you have all kinds of long-term injectables, you're looking at a BE study predicting a BE outcome from the in vitro or animal model. You are talking about individual responses that can detect.

So, if you have, like, say, pilot study that's 20 subjects, 15 subjects, or 12 subjects, the responses are varying very much in individual subjects in these long-term injectables. And until you reach to a point of a pilot study of 20 or something, you really cannot get what the meaning is.

And, when you use the animal models, you need to have a large number of animals to actually predict what the differences between RLD and test. Unless you have a 10 percent difference in the

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mean, you know, like in the formulations, really cannot say that you can go into the humans.

So that's where the animal models are getting, like, limited in usefulness. And the in vitro model has to actually predict the long-term ones that can take two months. And some of those things are difficult, and we're going into the animal models where the animal models have to be really large and also have to have a long-term animal studies. And it has to be a large number to detect the differences, at least 10 percent difference; otherwise, it becomes useless.

And the other thing we noticed with these things are that with a large animal, like the animal size and the volume of injection becomes an issue. In human, you are injecting large volumes like, say, whatever, you know, 1 mL, whatever, but the same thing you inject into a small animal, that the distributional things will become different.

DR. BURGESS: On the last point, the rabbit model is quite good. Small animal models like mice and rats, I agree. But once you get to the larger,

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the USDA species, then I think you're okay with that.

Also, in the animal models, I think they are easier to control than the human studies, maybe because of the way we keep the animals, house them, the way that we are injecting them, consistently, so we're not seeing such huge variation. And we were able to pick up the differences like in the microsphere formulations that we made that were Q1/Q2 to themselves, but had different in vitro release profiles. We saw exactly the same differences in the animal models. It was terrific, actually.

DR. VELAGAPUDI: Can you detect 10 percent?

DR. BURGESS: Yes.

DR. CHOI: I'd like to go on to our final proposed priority area. FDA is proposing conducting research on characterization of suspension and colloidal products. If Dr. Katherine Tyner could comment on considerations when determining the critical quality attributes of suspension and colloidal products.

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

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

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

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

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unintentional particles that are in your system.

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

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

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

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

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

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

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

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

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

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

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

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opinion, do you think that would help speed access to generic drugs?

DR. SRINIVASAN: Nice question, Stephanie. Actually, I'll go back to what Vincent was talking about. I was the reviewer and team leader for the iron for [indiscernible] actually when we approved. And the trick was constant communication.

And I think that's something, you know, guidances are great. You guys are doing a great job. But what we are missing is what we could do is pick up the phone and talk and say, hey, I'm not convinced with this; do you think you can do something else?

It was a collaborative effort and, you know, the only one with AB rating was passed. It was not just meeting requests, written responses, formal things, but a lot of informal interactions, which led to this, very similar to new drug and, you know, where people go. And a lot of things I'm hearing makes me feel that, you know, having that model would have been wonderful, where people could come and talk and, you know, have a much clearer

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idea of what needs to be done rather than just written responses, you know, and formal communications.

DR. VELAGAPUDI: I just want to bring one thing on the particle size distributions and the characterization. One thing for everyone, like, should one be looking at the time of the manufacturing versus at the end of stability? Do we have to, you know, follow the characterization at the beginning, at the end of stability studies, or just one is enough?

Agency?

DR. TYNER: I'm going to actually add on to that, even looking into stability, but also in-use stability tends to be very critical for these products.

DR. BURGESS: I guess you would need to look at the product and see what changes you have at the end of the shelf-life stability. And if there are, does it look like significant changes in, for example, particle size or some of the surface characteristics, then, you probably do need to

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follow up on that and do animal tests or other tests to find out if those differences are really going to be translated into the in vivo performance.

DR. CHOI: So, we will actually have to conclude this panel session and also the first session on complex drug products. Panel members and anyone else in the audience, if you have additional comments, please submit them to our docket.

We will now take a 10-minute morning break. Actually, 8-minute morning break. We will resume the workshop in this room at 10:25 a.m. Thank you.

(Whereupon, at 10:17 a.m., a recess was taken.)

DR. LIONBERGER: So, welcome back, everyone, to our second session. So, the topic for this section is Equivalence of Locally-Acting Drug Products. And we'll begin this session with a presentation from Markham Luke, who's the director of the Division of Therapeutic Performance, the Office of Research and Standards.

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So, welcome, Markham.

Presentation – Markham Luke

DR. LUKE: Hi. Good morning. Good morning, everybody. Welcome to the Food and Drug Administration, ladies and gentlemen, fellow scientists, fellow FDAers. I've been an FDA dermatologist for the last 19 years, and contrary to popular belief, dermatologists don't just prescribe topical products. We do prescribe systemic products, biologics, and a variety of complex, other complex products as well.

But, today my job is to talk a little bit about equivalence of locally-acting drug products. And for that, we're going to focus in on what are locally-acting drugs, first of all?

These are drug products that are not intended to be absorbed into the bloodstream. Their main site of action is local, like the skin, the mucosal surface of the nose and the lungs, the eyes, the ears. And some of these products that we've discussed do overlap with the prior talk.

In the past, FDA has relied on clinical

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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there was a draft guidance published earlier this year.

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

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

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

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approval of generic drug products.

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

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

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

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

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

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

But just briefly, development of

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

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

Public Comment Period

DR. LIONBERGER: Thanks, Markham.

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

So our first open public hearing speaker is

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Sid Bhoopathy from Absorption Systems.

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

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

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

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

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

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

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

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case because there is entrapment, there is biocellular formulation, and so on, that would limit the exposure. And this can look into both such attributes.

Now, I want to close with PK and local GI equivalence. PK, at least in our experience so far, this has better scalability. So the rate of permeation increased can better correlate to maybe a change in Cmax versus a 300 percent increased dissolution that has less in vivo translatability.

And when you do not have permeation and you're trying to assess a local effect such as biomarker upregulation, a simultaneous device like this results in a much smoother performance or potency profile. And this has widespread application. There are 10 GI products where we see its potential utility or 5 billion in sales, and about a million patients impacted, so this requires your collective support. Thank you.

DR. LIONBERGER: Our next open public hearing speaker is Dr. Vinod Shaw.

DR. SHAH: Thank you. And I appreciate the

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opportunity to give this presentation about the classification of topical drug products, a way forward to reduce the regulatory burden. The concept of topical drug classification has already been published in 2015-2016, but to provide a brief, the topical classification is a framework for classifying the topical drug products based on the qualitative and the quantitative composition, Q1/Q2, and the microstructure arrangements of the matter, and the in vitro release.

TCS when applied will help in approval of the generic topical drug products without conducting the in vivo studies, but assuring product safety and efficacy.

The drugs are classified into four different classes as you can see it here. Topical classifications within class 1 where the product is Q1, Q2 and Q3. Q3, again, is the microstructure, but we determined the in vitro release. And in most of the cases, including the microstructure, we have found that it correlates with the in vitro release of the dosage form.

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So, that would be the class 1, which would be eligible for biowaivers. And the class 3, which, again, the Q1/Q2 are different, but the Q3 is the same, and that can be eligible for biowaivers. Whereas class 2 and class 4 where Q1/Q2 is the same, but Q3 is different, microstructure is different, it would be class 2. And when everything is different, it would be class 4, and that would not be eligible for the biowaiver.

This classification is almost analogous, similar to the well-known classification of the biopharmaceutics classification system, which was established almost about 20 years ago. Yet, as you can see, for class 1 and class 3 BCS, you can get the biowaivers, class 2 and class 4, you cannot. They had to do the BE studies, whereas the same thing is true for the topical drug classification systems.

Right now, we have prepared 12 different formulations with the changes in the manufacturing process or the composition to the products in the classification of BCSI, II, III. We will be

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conducting the in vitro release, in vitro percutaneous penetration, Q3 arrangement, microstructure arrangement, rheology, and also we will be conducting the pilot BE studies using the DPK.

So, what I would like to propose and indicate and request the Agency to invite them to collaborate our efforts and to support the present work, which may facilitate the evaluation of the potential use of the BCS in the development of topical products and the regulatory evaluations.

This will definitely facilitate the generic product development. It will reduce the regulatory burden and assure the product quality across all therapeutic classes, availability of the topical drug products to patients and consumers at a more reasonable cost. Thank you for your attention.

(Applause.)

DR. LIONBERGER: So, our next speaker is Vatsala Naageshwaran from Absorption Systems.

DR. NAAGESHWARAN: Thank you for this opportunity. The focus of my presentation is to

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highlight how complex biology can augment formulation characterization and strengthen the scientific framework for assurance of equivalence.

So, there are numerous barriers for complex ophthalmic generic product development, and regulatory initiatives to include Q3 as an in vitro option for a subset of products is a step in the right direction. However, this is still very product specific and key questions about sufficiency of this approach still remain.

So Q1/Q2 formulations do not always have the same physical-chemical properties as we are all aware, and this type of chemical complexity can be elucidated through structural analysis and in vitro release testing.

However, formulations which meet the specified parameters can still have very different biological properties in terms of permeability, accumulation, distribution to target issues, efficacy, and even safety. And therefore, there is a requirement to elucidate biological complexity to address this residual uncertainty.

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So a lot of comparative studies to look at the underlying biology, which is based on a comprehensive understanding of the RLD is required to provide a basis for equivalence of biological properties.

So this needs to be integrated along with the physical-chemical characterization, and this type of strong scientific evidence is of efficacy and safety is what will provide confidence to the clinicians.

Ophthalmic drug products, unlike other pharmaceutical products, do not require human PK data as part of the approval because target ocular tissues and even surrogate tissues like aqueous humor cannot be sampled serially.

Even in the post-approval life cycle of a drug product, human PK data is not obtained. Instead, there's reliance on pre-clinical models whose ocular compartments resemble human and validated in vitro models which have established IVIVC.

So whether this is a model that looks at

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dilution and stability in tear film, or permeation across a corneal conjunctive or scleral tissue surface, or distribution to target tissues like iris ciliary body, or efficacy within a disease model where you're looking at quantitative endpoints like reduction in IOP, this integration of this data, you know, provides this basis for comparing equivalence of the biological properties that can be integrated with the physical-chemical characterization that Q3 provides. And further, it must be noted that there is IVIVC because these tests generate data for the RLD, for which you have human efficacy data.

So in conclusion, integration of various data parameters from physical-chemical characterization as well as biological characterization provides a performance matrix that gives us a deep understanding of a complex product and its process. Thank you.

DR. LIONBERGER: Thanks very much. Our final open public hearing speaker is Lisa Parks, representing the Association for Accessible

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Medicines.

DR. PARKS: I am Lisa Parks, vice president of sciences and regulatory affairs at the Association for Accessible Medicines, AAM. AAM represents the manufacturers and distributors of generic pharmaceuticals.

Generic pharmaceuticals represent greater than 89 percent of all prescriptions dispensed in the U.S., but account for only 27 percent of expenditures on prescription drugs, saving patients, payers, including the U.S. government, nearly $5 billion a week.

Today's generic industry includes a range of diverse companies who have become global leaders both in providing safe and effective medicines and pioneering nearly new treatment options for patients. Generic competition continues to play a vital role to improve access to pharmaceuticals and driving cost savings to the American patients and healthcare system.

This growth in the generic industry has led to the creation of thousands of jobs across the

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

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

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

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

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

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

(Applause.)

Panel Discussion

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

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

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

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

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

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

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

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

CMDR NGUYEN: Commander Josephine Nguyen,

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

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

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

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

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

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

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

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

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

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

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

DR. LIONBERGER: Ravi?

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

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

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

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

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

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

So as long as those features are identified

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

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

Do you want to comment on that, John?

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

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

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of what kinds of differences are allowable, thinking in terms of not only how they might work well, but also in terms of the failure modes of how they might be misused or inappropriately used such that they will fail because of that.

DR. CHOWDHURY: Maybe I can comment on this from the perspective of inhalation dosage form and perhaps also injectors. And it becomes complicated when you go across devices. For example, in the inhalation dosage form area, there are broadly two classes. One is metered dose inhalers, you just press and breathe. The other one is dry powder inhaler.

Now, for the press-and-breath metered dose inhalers, the instructions for use are pretty straightforward. You press, drug comes out, you inhale. So in that area, the device interface probably would not matter much. An expectation would be the instructions for use for an innovator, and a copy would be more or less the same if you introduce some of the complexity changes such as auto-inhaler mechanisms or some other complexities.

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In the dry powder inhaler area, these are very different. Each and every one of them has different unique characteristics of how you activate, how you inhale, how you prime for the next dose.

So in those areas, I think given what we just heard from Dr. Peters, I think the aim probably would be to have the instruction for use for the innovator and the generic be the same so patients can walk out with no training and go between the two devices and use it without any failures.

So that's the expectation. It kind of leads into the trap, if you would, copy of dry powder inhalers with complex design features may be very complicated. So that's why I think OGD needs to comment on the thing, would you allow variations on a risk-based approach. It is a risky place to get into, but if one is willing to get into, one can get there.

I think the general sense would be it may be a risky venture. And going into auto-injectors,

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for example, if it's an auto-injector for life-saving situations, if it's anaphylaxis, you probably would not want a copy of an innovator to have a different activation mechanism such as one by a press and another one is by a pressure of a button. A patient going through anaphylaxis would probably not be able to use them.

In a situation for a chronic use, every week you inject for whatever the disease be you may allow it if you allow the risk-based judgment, but it becomes very tricky because, as we just heard, if patients are given the choices to make mistakes, they actually can make mistakes. Thank you.

DR. LIONBERGER: Thanks.

So let's move on to our next topic, which is looking into topical dermatological products. And, you know, Markham outlined the characteristics of expanding the characterization-based equivalence approaches, so we welcome some discussion on this. And I think to start the discussion I'm first going to ask some of our -- we have a range of dermatologists on the panel -- some about the

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physical-chemical characteristics that are important to the patients. So if you can comment about which of those attributes, really, we should be looking for, for similarity in terms of patient substitutability of topical dermatological products.

DR. LUKE: I have two dermatology colleagues here, Denise Cook and Josephine, and we'd want you all to chat first about this, if you can.

DR. COOK: Well, I think. Denise Cook. I guess what would be important to patients in terms of topical drug products in general, is that they're easy to use, that they absorb fairly easily. They don't have to spend a lot of time trying to get the product to actually disappear on the skin surface.

So I think that the vehicle that the drug product is in is important for compliance for patients.

CMDR NGUYEN: As a medical dermatologist, I agree. Having the patient -- actually, it's interesting -- for men, the vehicle is more

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important because they don't like to use the greasy things; but for women who want to get the problem resolved quickly, the greasy formulations are actually more impactful and effective because they penetrate the skin barrier more quickly.

So, having the patient, so when I approach a patient, I have them understand the formulation, which one's more effective, but which one is also more easy to apply for the work day, especially for military members, they, it's hard to apply an ointment on and then put a uniform on because the ointment messes up their uniform.

Another important point is recognizing that skin barriers are different, specially, so you have a normal skin barrier and in many of our patients, like eczema patients, you have a compromised skin barrier. So when you apply a medication on a compromised skin barrier, because there's a break in the skin barrier, the medication can penetrate, oftentimes penetrate more quickly. And therefore, you can actually have blood levels of that medication. For example, in patients with eczema,

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severe eczema, studies have shown that application of a calcineurin inhibitor like Protopic, they were found to have elevated blood levels of that.

DR. LUKE: Just synthesizing from the two other dermatologists on the panel, the formulation of the product is important clinically because it's appreciated differently by different patients, and hence, vary the numerous types of formulation. And that makes, I guess, our job more difficult and that we have to have more formulations that we would address for Q3.

That's differences in the formulation, we have to get them as close as possible to the cream, but in itself, that look and feel of the cream should match the reference product. That's what I'm hearing. So if you're prescribing a cream, that patient is going to get something that is going to be that would need expectations to that regard.

DR. LIONBERGER: Ravi?

DR. HARAPANHALLI: I think, Markham, your summary of basically two approaches, I think it

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makes a lot of sense, Q3 characterization and performance approach versus totality of evidence approach and maybe a combination of two in reality that may be out there.

But the point here is that, yes, I think expanding the characterization-based methods or to clearly honing in on the Q3 aspect using various approaches, be it microanalysis, open flow, in vivo, or technique, all those combined, I think it would provide us a good picture of what different toolsets may be available for companies to really pick and choose for their particular product and show that they have a totality of evidence based on all these complimentary methods, in vitro approaches, to show bioequivalence to these topical products.

DR. LUKE: Right. Now, the notion of the chemical-physical characterization of the product is key there. For example, that Austrian cream that was studied, if you look at the viscosity of that cream, it's more like a lotion, and it behaved physical-chemically more like a lotion. So in that

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essence, you were studying a lotion versus cream even though it was labeled cream.

And this was an issue that -- I know, Vinod, you raised classification, but the heart of classification for dermatologic products is not Q1/Q2/Q3; it's what is a cream, what is a lotion? And there have been numbers of papers out there describing those specific product characteristics and what makes a cream a cream, what makes a lotion a lotion, and how similar do they have to be to fall within those characteristics.

And to get to a Q3 product, how similar, what gradation of lotion is sufficient to that a patient would not be concerned that they're getting something different from what the original intent that the prescribing physician was.

DR. COOK: Denise Cook again. Also, I think how similar the vehicle is to the innovator product is important in terms of efficacy of the drug product because we have found that, depending on the vehicle, it also influences how much the actual drug product either stays in the skin or is wicked

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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skin on your scalp or on your lower legs.

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

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

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

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

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we've evaluated clinically in saying, yes, we know it's efficacious and we know it's well tolerated.

Well, pharmacokinetics, I agree with you, has played a large role in making oral solid oral dosage forms bioequivalent and generics available, so that's one approach that we already have interest in, whether it's dermal microdialysis or even epidermal procedures with wicking or spectroscopic techniques.

Are there other techniques out there other than perhaps a combination of dermal or cutaneous pharmacokinetics methods, combined with an understanding of the dosage form, which may not be Q1/Q2, but still satisfies or addresses these other failure modes? Are there other techniques out there, that you're aware of, that we could be looking at for these non-Q1/Q2 products?

DR. LIONBERGER: I think in the interest of time and coverage, we'll move on to our next topic. Further comments, please submit them to the docket. And we'll have some additional discussion, I think, in our modeling and simulation topic because I'm

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going to ask questions about deconvoluting PK data in that session as well.

So let's move on to talk about inhalation products. So in inhalation products, the context is a little bit different. In the topical products, we have the Q3 approaches and you say, well, how can we expand them?

I think the question is a little bit different for inhalation products. With inhalation products, we have some more general weight-of-evidence guidance out there that aren't limited to Q1/Q2 formulations. But I think here, the challenge may be that the studies that we're asking are quite burdensome and challenging studies. So here, the scientific challenge is not just getting guidance out there, but moving towards more efficient guidance based on strong scientific principles.

So I formulated here the question about alternatives to the clinical endpoint BE studies that are currently part of the weight of evidence, but I'd like to open this up for some discussion

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around the inhalation area and looking at our guidances in ways that they can maybe be made more efficient, leading toward more access to generic drugs. So maybe we'll start off with Guenther.

DR. HOCHHAUS: I have a relatively simplified way of looking at inhalation and bioequivalence. And so for myself, one needs to answer three questions. One is, is the dose it gets in equivalent? Does it stay in the lung for the same period of time? And are the regional depositions about the same, central versus peripheral? And if all those three questions can be answered with yes, if the generic is about similar, then I think it's a good generic product.

Now, it's very, very difficult to answer all of those questions. And that is one of the reasons why the FDA says you have to do a clinical endpoint study. But the problem with the clinical endpoint studies is that, at least for some of the drugs -- and corticosteroids are probably one of the problem cases -- there's hardly any dose response curve.

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So if there's no dose response, if I even cannot distinguish between 100 and 150 microgram, I would also not be able to distinguish between a product that is more centrally or more peripherally deposited because --- and even any studies that show that clinical endpoint studies can catch that with marketed products -- you maybe can show it with very defined size products. But, so there is a problem.

The other problem is that those clinical studies, at least for corticosteroids, I think the number of subjects that you need are around, I don't know, 800,000 or so. So they are very, very expensive. And I can see the dilemma that the FDA is in because there will be certainties from non-generic companies' arguments coming, well, you need to show that they act the same way.

But I see maybe two developments. One would be the next one, where we can just say let's maybe try to move from those FEV1 studies to studies that may be similarly designed, but use less subjects, for example. And one might be able to go back to

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ENO using the study design that you use right now for FEV1 so that you don't do dose-ranging studies, but just use one dose, use ENO, which has less variability. And then maybe you can get the same result, probably also not showing a very strict dose-response curve, but the result would be there. You would have done a clinical study. I think that could be an intermediate way.

The next step I think is really to try to get rid of those clinical endpoint studies and use in vitro studies, which have been shown to have clinical relevance, and to use PK studies that can answer quite a number of those two questions that I started with.

It can certainly detect the dose that gets into the lung. It will detect differences in how long it will stay there. And hopefully, we'll be able to show also, at least for some of the drugs that dissolve very slowly, that also PK can pick up differences in central-to-peripheral ratio.

But I think in combination, good in vitro studies and PK long term might be a viable way of

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showing bioequivalence for this kind of --

DR. LIONBERGER: So, I'll follow up on the PK question. So, you know that in the European approach, they rely a little bit more on PK studies, but I think you've seen articles in the literature that talk about batch-to-batch differences in pharmacokinetic studies in the reference products. And that's been a long-standing challenge for the generic industry. What if my batches of the reference product come out different in my test?

DR. HOCHHAUS: That's not only a problem with PK, that's also a problem with clinical studies. That's a general problem of those batches that the innovator has come up with. There might be different designs and you might have to certainly think about PK study designs that look at different batches of the innovator.

DR. LIONBERGER: Badrul and then Charlie?

DR. CHOWDHURY: There are lots of things being discussed. I'll just try to be brief and maybe have some more people weigh in on this. On

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the question about alternates to FEV1, I think we have to acknowledge, FEV1 is very much truly tested, accepted endpoint. In situations where it works, it works very well. So that is not necessarily the problem.

If one has to look or looking to develop alternates to FEV1, probably some sort of biomarker kind of endpoint, which has been tried, and one can keep on looking for it. I don't think that really is the block of developing generics.

The one question we should step back and think about is how much clinical evidence do you need to show sameness? It goes back to what Guenther said. And I would say in many situations, probably one would not need to.

For example, in solutions, historically, one has relied on in vitro and not thought about needing a clinical study. It has been done in the past. Drugs have been approved, although there may be some changing course even in the solution area for steroids.

Now, for suspensions, you cannot

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characterize in vitro. I think the challenge there is more trying to characterize in vitro rather than try to do a clinical endpoint. And in some solutions, the science is lost.

So my preference would be really to get out of for the purpose of showing equivalence, clinical, but rely on in vitro, PK or some other methods.

Now, another which was brought up is many of the paradigms does not apply equally across inhalation dosage forms. So we're trying to fit the same paradigm for all the initial inhalation dosage forms -- MDIs, DPIs, nebulizers. They are not the same.

For MDIs, we got away with that because MDIs, if you all know, the propellant was close to 100 percent of the total delivery volume and weight. However, the chlorofluorocarbons CFCs are very, very uniform, so you didn't really have problems in characterizing those. You didn't need to.

When you get into the dry powder area, these

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are complex dosage forms, and there are actually biologic products in there, lactose. So dose-to-dose variability comes in, and you just cannot apply the MDI standards to DPI. It will not work.

So I think one of the research areas that one may want to look at the OGD side is trying to characterize the innovator product before setting out what our bounds would be. Because if you raise a bound for equivalence and test true batches of the reference product and they cannot pass with each other, that's an impractical standard.

So I think in some other areas, it just come up, like in the PK highly variable reference, just come up. In the biologic worlds, in the biosimilars, the different products just come up. So this is something of a research area to look into, it's that for complex dosage forms the same standards would not apply. Some different standards need to develop. It's not the problem of the endpoint; it's a problem with the standards.

Another, which is complex here to get

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into -- I'll just touch on and then leave out -- is we all know, all 85 percent of the products in the U.S. are generics. The problem is patients often complain, and they find differences, which are not there.

So it is patient acceptance, and I think it will become gradually heightened because, on the OND side, the Cures Act as we implemented it, and patient preference and patients' outcomes are part of the development paradigm. So this is another challenge to get into the initial dosage form, which applies all across. It's what to do with the patient perception of taking the MDI or DPI and not simply liking it. And if they don't, they'll find a difference. Thank you.

DR. LIONBERGER: I think we have Charlie, Larry, Sarah.

MR. DiLIBERTI: Very quickly, if you can detect product and lot-to-lot differences with a PK study, that's a much better metric than a clinical endpoint study. I would bet a million bucks that those lot-to-lot differences would never be

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detected in a clinical endpoint study.

Secondly, for the general class of inhaled corticosteroids, these drugs tend to be very insoluble and slow to dissolve. So in general, the rate-limiting step of the drug going from the crystal inside the alveolus to the central systemic circulation is the dissolution rate in the lung. So therefore, systemic PK is actually a very good measure of local drug action at the lung wall.

DR. LIONBERGER: We'll come back to you, Guenther. Larry?

DR. LEE: Sorry, Guenther, I go first.

But I think I agree. I'll keep it really short. I think we really need to look at the advances, the scientific advances in the inhalation area, especially from the particle engineering, device design, as well as the in vitro because I believe that we actually understand those much better nowadays, and that in fact, we probably know the variability-wide, where the variability coming from the PK in connection to the in vitro characteristics.

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So I think in this, at least from my perspective, I think we have much better understanding from the in vitro. I think we should give a little bit more weight on the in vitro finding.

DR. LIONBERGER: Sarah, then Guenther?

DR. YIM: So I just wanted to briefly say this is a big public health need in my opinion. I'm still educating myself on the nuances and complexities of these issues, and I know there must be a lot of them; otherwise, we'd have a lot more inhaled corticosteroid generics, especially in the DPI area.

So I'm not going to wax philosophic on the details, but I agree that we need alternatives to clinical endpoint BE studies. They're just very burdensome and expensive. So that's why we're here, and I'd like to hear more detailed ideas from the subject matter experts. Thank you.

DR. HOCHHAUS: I just, I fully agree with your statement, that it's not only burdensome and expensive, it's also the clinical endpoint

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strategy, at least for corticosteroids, as Charlie also said, you will not be able to differentiate between dose differences that you would otherwise feel as significant.

What Rob just said with respect to comparison of the FDA approach compared to the EMA approach, I think a weight-of-evidence approach using different tools at the same time is very important. And the use of in vitro plus PK certainly will give you much, much more information than just doing a PK study when the in vitro studies fail.

In addition, we can also look for additional in vitro studies. And we just said that the regulating step of, might be the dissolution. And I think it's a very, very good idea that we look into the area of dissolution rates in the area of inhalation drugs, to use that as an additional endpoint, an additional point to potentially look for differences between generic and innovator.

DR. LIONBERGER: Ravi?

DR. HARAPANHALLI: Yes. I want to touch

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upon Badrul's point that a generic device may or may not be acceptable by a patient because they're used to a design. And that connects back to John's point earlier that there could be misuse scenarios.

But the point here is that, typically, a lot of human factor assessment goes on. Generics don't suddenly come up with their device and say this is it. A lot of development goes on. They are developing their own device, and they are also comparing with their innovators, and formative studies, summative studies, all that goes on.

When we talk about misuse and risks, it should be related to risk. It doesn't mean that an innovator doesn't have any risk. They have their own risks, too. So when we compare that risk versus this risk, you should be putting that perspective, and then decisions should be made, whether a generic should be approved or not.

And whether somebody likes it or not, let it be left to the market. So once all the things are addressed and it's deemed to be equivalent, then let the market play it out, whether somebody likes

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that design or not. So thank you.

DR. LIONBERGER: Any further comments on inhalation products?

DR. LUKE: The issue of biomarkers, I think, we have -- especially with these, with drugs that work in more chronic fashion. Is there room for that? And also, radiologic studies, looking into, there have been tremendous leaps and bounds on software analysis of a variety of radiologic images. Is that another reasonable approach to looking at, maybe making FEV studies better and less variable in their outcome?

DR. CHOWDHURY: I can probably just touch on this a bit. I think people are very interested in developing biomarkers, and there are actually many that are being used in different investigative settings.

The problem that comes up is that, it doesn't look like these biomarkers are yet a very sensitive measure of a corticosteroid effect that one can pick up in a clinical setting as a potential difference.

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Eosinophil counts have been looked at in the past, investigated extensively, and did not seem to pan out that well. Exhaled nitric oxide, which was at some point a fashion to go after, I think OGD did a very nice study trying to look for those differences, it did not pan out the [indiscernible] either.

Now there is some interest in moving out of the human lungs in our division, lung situations [indiscernible] measure resistance and flow in their setting. And those are also alternate approaches to look for.

So I think there's interest in biomarkers, but it's not yet there to pick up differences. So I really go back to see if there is any ways of using less of clinical for declaring sameness and if those can be addressed in vitro. We seem to be progressing, as we heard earlier, a bit faster. Thank you.

DR. PETERS: I'd like to go back to one thing that Badrul said earlier. As we look at these products, we have to keep in mind that some

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of them are for prevention, some are for symptom control, and some are life saving.

So from the standpoint of public health, it's our duty to be sure that there are no significant differences that would put patients at risk because that's the point of the public health.

So putting something out with a statement like, "Let the market decide," is not going to be something that would really be doable by us. We would have to be assured that that risk-benefit ratio is the same as it is for the RLD. And that's part of the program that we have with generic drug surveillance now, is being sure that we learn more about exactly what are those significant differences in a risk profile as well as in the efficacy profile.

DR. CHOWDHURY: I would like to touch on to that. That's a very important point that often gets actually lost. The human factors studies are very useful, absolutely necessary and should be done. But for some life-saving situations, where a patient is to use the drug, you cannot replicate

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that in a human factors study.

For example, simply an MDI if it works perfectly well if you put it straight out, vertical, and use it, it works. However, if you put it at an angle, it does not deliver. It's very difficult to pick it up. In vitro can pick it up. Human factor may or may not.

The person is waking up in the middle of the night, short of breath, and goes for the inhaler. If he cannot use it, ends up in a bad situation. And lying down using it horizontally, if the drug is not going to be delivered, he just can't accept that.

So these are very complex situations, and I fully agree that it needs to be looked at in a very detailed fashion. We don't want to put out something which may be potentially life threatening if not used properly or the patient is thinking using properly, but the device features doesn't allow the drug delivery properly.

DR. LIONBERGER: The last comment from Sarah.

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DR. YIM: Then circling back a little bit to question 1 and acceptable design differences and the issue of substitutability, I think this all sort of ties in because as hopefully we get more of these combination products out on the market, the more tweaks we're seeing in design differences out there, the more substitutability issues might arise, right, where it won't be necessarily patient preference that's driving what device they get. It's going to be what's on the formulary, what's on the formulary that month, things like that.

So it gets to be kind of a complex issue, how much differences are you going to actually start allowing in the combination products that are going forward for the generic combination products?

DR. LIONBERGER: Let's change topics. A little bit, talk about a different product category and talking about ophthalmic products. And here again, a question for the panel, moving toward in a similar way to the topical products, expanding the space for ophthalmic product characterization.

So again, ophthalmic products are

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regulations, so they have to be Q1/Q2. So that's off the table. But we heard discussions from Bob Bellantone this morning about in vitro release tests, that if you have a good release test, you might be able to say well I have a Q3 difference, but it's acceptable because it meets an important model of product performance.

So I'm interested in a discussion on the ophthalmic product category.

MR. DiLIBERTI: All right. I'll start. So let's talk not about the emulsion formulations, but about the suspensions, simple suspensions, drug crystals in an otherwise clear liquid.

I'm not sure what you gain by any human studies on those beyond what you already find in vitro. You can characterize those as well as anything else. And to me, to do a rather onerous aqueous humor PK study seems a bit over the top.

DR. LIONBERGER: Larry?

DR. LEE: Yes. Rob, I think this is a good idea, but I think the key question -- maybe OGD in the future wants to look at it if you do decide to

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go to the in vitro route -- you try to have a more systematic approach to decide to determine what is the full orthogonal set of in vitro characterization you need to do in order to demonstrate Q3. I think there is a different way to do it.

One way is you have to understand the relationship between the manufacturing as well as certain attributes, changes in certain attributes. So I think this is the area that you may want to -- I recommend OGD will probably want to look at it if you want to decide to go forward using an in vitro approach.

DR. LIONBERGER: Let's take it to a little bit about the suspension characterization of the suspension products. Are there any scientific gaps that would prevent us knowing attributes of ophthalmic suspensions that are clinically relevant?

DR. LUKE: I just want to point out that when you discuss the full space of ophthalmic products, and the folks in the ophthalmic group

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would agree, that it encompasses products for use in any part of the eye, including the area around the eye, some of which is skin, or lash, or hair. And what is your target organ or target tissue is going to vary depending upon what your product is, what your formulation intent is.

So if your target is the hair roots, and you're trying to grow lashes, versus the use of the product to affect the iris or looking at intraocular pressure management, those all have different target organs and may require different approaches to looking at both clinical B from what we've seen and also perhaps penetration of the product into this space where the site of action is.

DR. LIONBERGER: Also interested in comments on -- you've talked about both dermatological and ophthalmic products. Both sometimes have semi-solid products that have similar characterizations, some have suspension products.

So are there common themes that we can learn across the Q3 characterizations that can be

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generalized? Would there be interest from the industry in more general guidance on Q3 characterization that would help that in general?

So we're open to comments on that. What could FDA do to help generalize these Q3 approaches across a broader range of dosage forms than just one product-specific guidance? So Larry first.

DR. LEE: I think one thing you may want to look at is the ability to characterize certain particles in the mixture environment. I think, for example, let's say you want to determine particle size in the presence of other excipient. How are you going to do that? I think that is something that from the analytical perspective, you may need to overcome some of these challenges.

DR. LIONBERGER: Charlie?

MR. DiLIBERTI: I think suspension, simple suspensions where it's just drug crystals in an otherwise clear liquid, are low-hanging fruit here. I think we have easily the analytical technology to characterize those incredibly well. So I would recommend focusing on those.

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DR. LUKE: I would say, for the ointments and the creams that are used around the eye, a very similar approach we are taking for dermatologics could be applied. Essentially, once you characterize a cream, and we haven't had the tools to do so, I think we can apply them across the panoply of those products.

DR. LIONBERGER: So we have about five minutes left, so I want to just tee up a few final -- and give you the opportunity for one last comment in this area. Some things we haven't covered and talk about potentially are for nasal products, and if you have any specific comments and some similar issues related to I think the inhalation areas, where we have outlined weight-of-evidence approaches.

There may be an opportunity to move toward more characterization-based approaches for the nasal products or just any other attributes of the locally-acting products that you think we should consider in terms of our research activity.

So it's a pretty broad comment, and I open

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

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

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

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lunch, it will be available at the kiosk. There's also lunch rooms. If you go out the hall and behind here, there are rooms with tables set up for lunch. You don't have to sit in the hallway, although it is a quite nice day, and there is an outside park as well outside the doors there as well.
So we'll be back at 1:00. Thanks, everyone.
(Whereupon, at 11:59 a.m., a lunch recess was taken.)

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A F T E R N O O N S E S S I O N
(1:00 p.m.)
DR. LIONBERGER: Welcome back, everyone, to our afternoon session. The topic for Session 3 is Therapeutic Equivalence Evaluation and Standards. And everything that we're not talking about in any of the other sessions fits into this category.
So to provide the introduction, I'd like to introduce Myong-Jin Kim. She's the deputy director of the Division of Quantitative Methods and Modeling in the Office of Research and Standards. So welcome, M.J.
Presentation – Myong Jin Kim
DR. KIM: Thank you, Rob.
My name is Myong-Jin Kim. I also go by M.J. in case it's hard to pronounce my name. I hope you really enjoyed the weather outside during the lunch hour. It's one of the most gorgeous days that we have ever seen recently.
So I'm here to give you some FDA research update for the therapeutic equivalence evaluation and standards. For my talk, I'm going to talk

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

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

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

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

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

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

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

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describe how this drug can be administered via enteral tube administration, and a risk of clogging may have been studied under certain specific circumstances, or it may describe a drug interaction with proton pump inhibitors where these drug interaction findings can affect the drug released that is based on a pH-dependent mechanism.

In order to ensure the same level of safe and effective use of generic drugs as the reference product, the question is, do we need more in vitro or in vivo BE data?

One approach to address these issues in BE assessment for solid oral dosage form is to utilize a modeling and simulation method. Dr. Liang Zhao will represent a quantitative method in the modeling approach in support of the GDUFA regulatory science research program in more detail in a later session of this public workshop.

But briefly, FDA uses modeling and simulation, and virtual BE simulations to examine these cases to guide regulatory standards. Sponsors are encouraged to utilize these modeling

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and simulation tools in support of proposing alternative BE approaches.

While the PBPK model approach is often used in the new drug development arena, this approach can support the regulatory decision-making for generic drugs as well. They range from identification of clinically relevant specification of in vitro tests such as dissolution and risk assessment for new formulations with release mechanism changes; BE extrapolation from healthy volunteers to specific populations; waiver of in vivo studies using virtual BE simulations; and assessments of effects of PPI on drug exposures, especially for formulations that are pH dependent.

In addition to PBPK, the quantitative clinical pharmacology approach is useful BE assessment of solid oral dosage forms. Its impact can range from PK matrix determination for BE such as evaluation of partial AUC, model-based BE assessment, and BE study simulations.

This slide shows a list of some research projects, and they range from NTIs, PBPK for

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systemic and locally-acting products, to model-based BE assessment for PK and performance. Dr. Liang Zhao will go over these in more detail in his presentation.

With all this in mind, for our panel discussion, we would like to hear from you how we can integrate predictive dissolution, PBPK, and PK/PD models for decision-making about generic drug BE standards and what would help to reach this goal.

Let's shift gears to our last topic, BCS class 3 drugs and biowaiver for solid oral products. In May 2015, FDA published a revised guidance for waiver of in vivo BA/BE studies for IR solid oral dosage forms based on a BCS. This guidance includes biowaiver extension to BCS class 3 drug products.

As you know, biowaivers can be granted for highly soluble and highly permeable drug substances in IR solid oral dosage forms that exhibit rapid in vitro dissolution. For BCS class 3 drug products, in order to be qualified for a biowaiver,

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the drug substance should be highly soluble, and the drug product is very rapidly dissolving. In addition, BCS class 3 test drug products must contain the same excipients as the reference product.

The composition of the test product should be qualitatively the same and quantitatively very similar to the reference product. This is due to the concern that the excipients can have a greater impact on the absorption of less permeable drugs.

This objective of eliminating the need for unnecessary in vivo BE studies. Extension of biowaivers to BCS class 3 drugs was included in the guidance as stated in the GDUFA 1 commitment letter. However, there is a concern that the current BCS guidance on class 3 waivers is not helpful to the generic drug industry because most generic solid oral products use different excipients than the reference product.

I have listed several research ideas here, and we would like to hear from the panel how we may expand BCS class 3 waivers to non-Q2 formulations.

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With this in mind, we do have three priorities for the panel. One is in vitro alternative to in vivo nasal studies for abuse deterrence of solid oral dosage form of opioids.

The second one is how do we integrate the predictive dissolution, PBPK and PK/PD models for decision-making about generic drug bioequivalence standards. And lastly, how do we expand BCS class 3 waivers to non-Q2 formulations?

DR. LIONBERGER: Thanks very much, M.J.

Our next speaker is representing the generic industry, so this is Siva Vaithiyalingam. He's from Cipla, and welcome, Siva.

Presentation – Siva Vaithiyalingam

DR. VAITHIYALINGAM: Thanks very much, Rob. I appreciate it.

Good afternoon, everyone. My name is Siva Vaithiyalingam. I am from Cipla Laboratories, and many of the discussions, many of the things that I wanted to speak of have already been covered by M.J.

Thank you, M.J. You did a great job. Thank

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you, Rob, for your introduction and bringing me here.

Before we started on this project, M.J. and I had a good discussion, and we had four different topics to talk about. The first one was essentially, the abuse-deterrent products, opioids. The second one was on the partial AUC. The third was on the BCS 3 regs. And the fourth one was the NDA drugs. So these are the four topics, essentially, we discussed about the talk in this workshop.

The first one was on the abuse-deterrent opioids. And currently, as M.J. said, there is a guidance, but the guidance is primarily focused on the new drugs. As of now, the guidance is focusing more on the new drugs. So what we really want is pretty clear, something for the generic drugs.

In the typical abuse, the product is crushed, snorted, injected where the drug is available for systemic circulation in a rapid manner in a high intensity. So with that in mind, there is not much of hope in the guidance to the

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generic industry in terms of how to develop, or perhaps most importantly how to test to the point where the generic product is as abuse deterrent as the reference, which is the key, isn't it? Apart from being equivalent orally, it has to be as good as the abuse deterrent.

So I think, from that perspective, perhaps our request is to have a good amount of research focused on establishing the conditions, establishing the tests that are required for demonstrating the sameness in the abuse-deterrent potential between both reference and test.

Essentially, I'm summarizing what I said. In the research areas need to be focused to the extraction procedures that mimics the real-world techniques that folks use to extract the product, extract the API from the product. And then the endpoints, the extraction procedure sometimes is so long, they do end it.

So that kind of information would be really helpful. The guidance would be really helpful for the industry.

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The next topic is on the partial AUC. Partial AUC is a really challenging thing for establishing the bioequivalence evidence. On many occasions, what we've found is that the guidances are out in a very late stage, so the first and the foremost thing that we request is the guidances on partial AUCs to be on a timely basis.

Secondly, we request the agency to put a lot of resources on sound scientific principles in terms that the PK profile and partial AUC should completely correlate with the therapeutic outcome in the patients. If these things are not considered perhaps as you would easily imagine, BE metrics, which is the partial AUC for certain drugs, may cause a significant generic barrier.

The third topic that I wanted to speak is on the BCS 3 waiver. In BCS 1 compounds, at least we have a good grip on it in terms of the biowaiver. And I'm very glad that the agency is looking into BCS 3 waiver also. However, as M.J. pointed out, the major obstacle in this BCS 3 compound is ensuring qualitative and quantitative sameness for

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

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

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

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

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and Honda, and how do we go up to that destination. So how did they go to their destination, the RLD, to go to the sameness of the product? We can learn a lot.

The second thing is, I think the agency has been doing very good research here, understanding all the variables, the product, and the process variables for the data that is not submitted to the agency without a response. So this is an example of these three publications that are listed here.

So you are saying these publications here vary our understanding of the formulation variable, the process variable, the analytical characterization that will help set the standard. So I think this is the internal standard that research is needed.

But honestly so, it has taken about five years -- I was involved with this. It has taken about five years to understand this one product of OxyContin, and really we haven't spent a lot of time because the product design and compositions could be very complicated, coating methods, and

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goal is [indiscernible] combination.

So this work, if the agency tries to do it, it might take them another 15 years. If you don't want to wait for 15 years for the approval of other generics, perhaps you can request -- I mean, you can solicit external help here for critical material attribute and critical process variables of all products, all the 10 products.

So one is understood. The other nine products, you can seek external help. The nasal irritation studies, I think M.J. has asked for this question, can be easily understood. And linking the critical quality attributes with category 2, 3, and 4. That's an important aspect there, but you can seek external help.

I think NIPTE has been doing a consortium of 17 different schools. They've been working. They've been doing a lot of work, and they really have a lot of expertise. Purdue and Maryland has already done some of the work for ADF. So NIPTE can do the study. Thank you all very much, and I will stop here. Thank you.

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(Applause.)

DR. LIONBERGER: Our next speaker is Dave Schoneker, representing IPEC-Americas.

MR. SCHONEKER: Good afternoon, everyone. IPEC-Americas appreciates the opportunity to provide public comments at this meeting. Given the increased understanding of the importance of excipients to the quality and substitutability of all generic drugs, we'd like to make the following two requests, targeted at increasing FDA collaboration and transparency with all drug ingredient suppliers, not just API suppliers.

Much discussion occurred this morning about API CQAs. As you've heard from previous speakers, excipient CQAs are just as important and sometimes more important.

So request number one is that IPEC-Americas would like to recommend that FDA collaborate more directly with members of the excipient industry to ensure improved transparency in selecting the specific studies to support and interpreting or implementing results from the studies.

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The need for better understanding of excipients, especially polymers and their role in drug products, have triggered more technical questions being asked of suppliers than in the past. However, most excipients are produced by chemical companies whose primary focus is not in supplying to the pharmaceutical industry.

R&D resources in the chemical industry, allocated to fundamental research, have been significantly reduced in the last decade. Therefore, if FDA is expecting a more fundamental understanding of excipients and their CQAs, then the FDA regulatory science initiative program will need to help fund fundamental studies and research in this area.

So IPEC-Americas is offering to collaborate with FDA early in the process for any excipient related projects. IPEC-Americas' subject matter experts can contribute valuable knowledge and experience to help FDA better select and design projects to achieve their objectives. These experts would also be instrumental in assisting

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

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

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

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

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But at any rate, the next series of studies is MRI studies of the human gastrointestinal tract, where we actually measure fluid. We can also give dosage forms at the same time, and we're cross-validating the manometry method of motility, which is the classical motility method, measuring the pressure contractions in the intestine along with the MRI studies, which are more generalizable. We can do patients, we can do pediatrics, so I think there's a bright future here for MRI studies.

Gastrointestinal variables to drug absorption -- is it red? Okay. I'm done. My slides will be available. Thank you.

DR. LIONBERGER: Our next speaker is Dr. Jim Brasseur from the University of Colorado.

DR. BRASSEUR: Thanks. Gordon said only three minutes before I came out.

All right. So I'd like to continue -- if I could have the first slide. I'd like to continue from Gordon's talk. So I'm part of the group at the University of Michigan. I'm an engineer, but I've been working in gastrointestinal physiology

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and mechanics for the past 30 years with regard to drug absorption and release in the gastrointestinal tract.

So one of the points that Gordon made that they were carrying out these studies at the University of Michigan in which they are measuring in vivo quantities related to drug dissolution and absorption. For example, here I'm plotting in the right hand a single location in the intestine, the variation in the pH.

You can see this is for ibuprofen. It varies around the pKas, so as a result, solubility varies dramatically with time as well. This is also true along the gut, so if you measure other variables such as concentration along the gut, for example, and in the different gut segments, and pockets, and so on, they vary dramatically, both in the liquid form, on the left-hand side in the jejunum and the duodenum, and on also the solid form as well on the right-hand side. And as Gordon has said, the solid form is lasting a lot longer than had been previously appreciated.

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Why is that? Well, to a large extent, it's because of the motility in the intestine, which is extremely complex and has various components to it. So in the middle picture, I'm showing Ehrlein movie of the fed state in the dog. And you can see how the changes in the volume of these pockets dramatically is driven by the contractions of the muscle wall, which is what's meant by motility.

Now, that moves content, including particles and drug concentration, to the wall of the intestine, where it can be absorbed. So if there's a lot of variability in the motility, there's a lot of variability in the absorption correspondingly.

It's more complex than that, however. At the lower left, we are showing the fed state, and in the middle, the fasting state. These are very different and, in particular, for example, in the fasting state, there's two kinds of peristalsis. One is a global peristalsis, which follows the MMC3 contraction, and then there's local peristalsis within the global peristalsis. And these are very different speeds, and one can go antegrade, one can

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go retrograde, and so on.

The water pocket volume does vary tremendously as well. Luca Marciani is part of this group as Gordon mentioned, and he's measuring huge variability in the volumes. So if you imagine variability both in the content as well as in the volume, you get huge variabilities in concentration as well. So there's pretty much variability in everything.

So when one is doing computer simulations -- this is computer fluid dynamics, computational fluid dynamics -- one has to take into account these variabilities to predict both the release and the absorption in the intestine. And these variabilities will create different levels of absorption with time and along the gut and so on.

So I guess the take-home message from this short discussion is that modeling frameworks, in my view, in the future need to take into account the stochastic nature of the drug release absorption process. It should incorporate variability both in

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the model as well as in the predictions. Thank you.

DR. LIONBERGER: Our final speaker is Robert Page representing American Heart Association.

DR. PAGE: I want to thank the committee. Again, my name is Robert Page, and I'm a professor at the University of Colorado. And again, I'd like to thank the committee to provide public comment on behalf of the American Heart Association.

I'm going to take a little different stance, so you're probably asking, oh, my gosh, what is he talking about? But as an evidence-based patient advocacy organization dedicated to improving cardiovascular health for all Americans, the AHA provides a unique role, and it has a unique role to play in advocating both for the science perspective, but also the health policy viewpoint so that treatments are available, affordable, and assessable.

As you've heard today many, many times, the rising costs of prescription drugs is an important concern, and in order to ensure that drugs are cost

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effective, we find that generics have been one of those key sources.

The use of generic drugs has led to substantial cost savings, and it has been brought up that 88 percent of dispensed prescriptions are generic and that only 28 percent of total drug spending goes to generic drugs. However, I'm going to advocate on behalf of the patient today here at the FDA in the case of certain generic medications.

We have certain vulnerable populations, heart transplant, post-myocardial infarction, stroke, or heart failure in which a 30-day supply of evidence-based pharmacotherapies are unaffordable. For example, the out-of-pocket cost for several evidence-based pharmacotherapies that have been generic for several years is that of digoxin, metoprolol succinate, and torsemide. The cost of a drug that was $1 is now about $40. And when you're on a Medicare part D plan, that's a lot of money.

Colchicine, which is used to treat gout, went from just a dollar to over $150 for a 30-day

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supply. Why is this the case? We know. And again, this committee has identified that already. Smaller markets tend to attract fewer competitors. Number two, mergers and acquisitions are occurring. And for these reasons, consolidation is a concern with regards to our patients.

The impact that we are seeing from a clinical perspective within the community is the fact that higher generic prices have adverse effects upon everybody, from providers to patients. Therapeutic advances in cardiovascular and stroke treatment have greatly enhanced the lives of our patients. And for that, I really truly want to thank the Food and Drug Administration. But affordable access to these medications, specifically generic medications, is crucial if you're going to prevent cardiovascular disease and stroke. Therapies aren't effective if you can't take them.

So with this in mind, as the FDA ponders with regards to its research questions, I'm going to pose a public health question. First of all,

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from a health services perspective, we should be asking which of our vulnerable populations are affected most by the rising price related to generic prices?

Within these vulnerable populations, how has rising generic prices impacted health outcomes from both a health resource as well as a cost burden on all stakeholders? And finally, the American Heart Association is willing to collaborate with the Food and Drug Administration in order to address these issues.

I want to thank the committee for their time.

(Applause.)

Panel Discussion

DR. LIONBERGER: Thank you very much. So that concludes the open public hearing part of this session, and now we'll move to the panel discussion. So I'd like the panel to just briefly introduce themselves and their affiliations, starting on my right.

DR. BYRN: Stephen Byrn from NIPTE, and I'm

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a professor at Purdue.
DR. CONNOR: Dale Connor, director, Office of Bioequivalence, OGD in CDER.
DR. GANG: Lucy Fang, team leader, Division of Quantitative Measures and Modeling ORS OGD.
DR. HARAPANHALLI: Ravi Harapanhalli, senior vice president, global regulatory affairs at Amneal Pharmaceuticals.
DR. GOBBURU: Joga Gobburu, University of Maryland.
DR. MEHTA: Yes. I'm Mehul Mehta. I'm a division director in the Office of Clinical Pharmacology, Clinical Pharmacology I, New Drugs.
DR. POLLI: My name is Jim Polli. I'm a faculty member at the University of Maryland.
DR. SCHMIDT: Stephan Schmidt, associate director for Center for Pharmacometrics and Systems Pharmacology at the University of Florida.
DR. SEO: Paul Seo, division director, biopharmaceutics, Office of New Drug Products, Office of Pharmaceutical Quality.
DR. STIER: Ethan Stier, division director,

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

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

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

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interest, but I think we want to maybe step back and say what is causing the abuse-deterrent epidemic or the problem and its deaths. And I think it's mostly deaths by injection.

What's basically happening is people are injecting medicine in their body, and they don't know what the dose is. And obviously, these are potent drugs, and they suppress respiration.

So what I would like to do is take off on what Mansoor was talking about. I think we need to focus on sameness determinations and also barrier goals in the data submitted, especially related to process and formulation because the drugs that we're dealing with are extremely water soluble.

So we don't really have a problem with anything. They're just very water soluble. So what we need to know is how to formulate it and how they're made. I think we need excipient understanding from the speaker. I think the excipients are playing a role, and we need to know what that is.

The last thing, I was one of the

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investigators on the FY13 project, and it's out of date now, four years old. I think there was only one product when we started that investigation.

So we need to, again, continue to investigate these products. It's a very interesting area.

DR. LIONBERGER: Ravi?

DR. HARAPANHALLI: First of all, I think the new guidance that came out last year, the draft, which we believe will be finalized this year, it's really a great step forward, and it draws from the original guidance that was geared towards new drugs.

Particularly, I like the idea of D versus R versus C, the concept of a control as a way to differentiate different tests and statistical criteria.

Now, coming to this critical question, what I feel is somewhat less focused in that guidance is that it talks about the particle size ranges after you grind material for certain defined amount of period. And based on the sieving, you decide the

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study, and then you compare both RLD and the test product. But it doesn't quite go into the fact that the particle size itself could be different for the API. It's possible that drug could come out, and it could have its own unique particle size distribution that's not represented by the cross-measurement that we typically do, and that could directly impact your in vivo nasal studies.

So if we can have a better in vitro alternative where we can selectively measure the API particle size in the ground material, maybe MDRS or some other techniques, perhaps that would serve as surrogates for doing such in vivo nasal studies. So that's something that I think research would be needed in that kind of area.

DR. LIONBERGER: One follow-up, one specific area under the nasal abuse that's of potential research interest is in the role not just of the physical barriers, but of the aversive nature of the components.

So any comments on how to evaluate that and I think whether other components in the formulation

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may have an impact on the drug aversion?

DR. XU: For the aversive effect, we're trying to look at it as a purely technical consequence of the material triggering some reaction. But in a lot of ADF formulations, use of the polymers, especially high-molecular polymers can also introduce physical discomfort, which in a way also is introducing the aversive effect even though not specifically aversive agent.

But I guess the challenge is how do you quantify the irritation or potential of molecules of materials without doing in vivo study? And is there any way to come up with in vitro studies or even somewhere in between, intermediate, to look at the irritation potential because this is related to physiological response of the physiology as well as the psychology of the sniffing the material into the nasal cavity.

DR. HARAPANHALLI: By definition, the aversive agent is meant really to inflict certain discomfort when somebody tries to abuse it. So that said, I don't know if there can be any

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alternative in vitro or animal models that can reliably predict that. It is something very unique to humans that they either like it or dislike a particular formulation when they try to abuse it.

So I'm not very sure that there can be any better alternatives other than actually doing a usability-type study.

DR. LIONBERGER: Just a question, as you look ahead, are there any other areas -- I mean, we focus here on what are in the currently approved reference products? That's' the starting one. Are there any sort of research frontiers that we should be looking ahead to prepare for the next generation -- I think the question was get the science done ahead of time.

So let's do some horizon scanning and say, what are the emerging areas in abuse-deterrent formulations that you think need to be prepared for the next generation of generic products?

DR. BYRN: Of course, being a professor, I think we need to look at things in the future. But let me suggest that there might be a way to do

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this, which would be to look at patent applications, because I'm guessing that people are putting in things pretty quickly after they discover an approach.

So there may be a strategy to review those documents and then to make a determination of which of the approaches appear to be most likely to move forward and to carry out a study following that.

DR. XU: As we understand, in vivo studies are quite difficult to conduct, especially related to ADF studies because if you are aware of the labeling guidance for the ADF product, there is category 1, 2, 3, 4 studies.

But as you move up the categories, they're difficult to increase because it's involving human subjects, which means how to evaluate the effectiveness of the abuse deterrence potential in a human liability -- drug abuse likeability study.

So certainly, if there are in vitro tools available, it will help to shorten the time or save the cost of conducting the in vivo studies. And also, we know the AD properties is part of the

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product qualities due to the formulation design, due to the manufacturing processes.

It's suspected to be intense throughout the product shelf life and during the stability, so how do we determine the AD property and AD potential of postmarketing? So certainly, if there is in vitro tools, in vitro methodologies available, and preferably standardized in vitro methodologies available, that will help to ensure that the AD properties can be maintained even postmarketing.

To extend on that, also the category 2 and category 3 studies rely on the category 1 study, which is in vitro. So how do we find vast in vitro markers or the surrogate properties in order to be more representative and then to give better information to guide the category 2 and category 3 studies? That will be I think the very important to look in and to do more research.

DR. LIONBERGER: One final discussion point of this is, we've got some expertise in PK/PD modeling here. Can we talk about what are some of the things we should be looking for as we try to

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understand the PK/PD relationships for abuse-deterrent formulations Sometimes all of these products get labeled claims by a drug liking study, which is really a pharmacodynamic endpoint that's the basis for approval.

So comments on how our understanding about the pharmacodynamic effects of this drug may help pathways for generic products, so I would appreciate any comments on that, just any member of the panel.

DR. SCHMIDT: So maybe it would be important to look at this not necessarily from a switchability point of view, but from an exposure response point of view, saying which processes play a role. So we have of course in the practice setting also the potential of drug-drug interactions of uptake or drug-drug interactions in the field with uptake across the blood-brain barrier.

For example, for oxycodone, you have 2D6 also in the brain. And if you have a combination in the practice setting that would inhibit, for

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example, PgP in the blood-brain barrier, plus you have flagged a subpopulation that would be a poor metabolizer or other metabolizers for 2D6, that may play an important role.

Again, this is not necessarily a switchability question, but I think, particularly for colleagues at FDA, this would also provide an opportunity to learn from -- that would provide an opportunity to learn from the colleagues at the Office of Clinical Pharmacology, for example, because, I mean, they look into this type of question for new drug applications anyways.

DR. GOBBURU: I see the role of generalizability. We can use quantitative approaches for that in two dimensions. One is going to be in terms of understanding the relationship between the level of abuse deterrence and its impact on the potential development of dependence and such.

Understanding that relationship will give us one dimension of specs in terms of what type of abuse-deterrent characteristics would lead to

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clinically meaningful differences, especially on the lower side, not so much on the higher side.

The other dimension would be to understand the contribution of the different excipients that are used for making the product abuse deterrent and how that's impacting the product performance. So it's the excipients to the product to some kind of a patient sign or symptom with respect to abuse.

If we can understand that -- and in fact, that's the only way I see, actually, that we can solve this problem of substituting in vivo studies with the in vitro or in silico studies. If you think about it, maybe it's a different take by the agency, but the stakes of making a mistake is pretty high, and people are nervous about it, both public as well as the government.

So until we have adequate experience, but with a commitment to develop such an understanding, asking more studies, I don't see that as unreasonable.

DR. POLLI: I would just totally agree with that. So I'm going to make comments even though

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I'm just not an expert in this area. And what I was thinking about was Dr. Amidon's slide, which was very new to me, about ibuprofen is very familiar, and we like to think we know a lot about maybe the absorption of that drug, but maybe we don't know so much.

So I would agree that, given this issue, yes. Maybe in vivo studies are difficult to do, but isn't this topic worth it? And quite often, in formulation, we probably don't do enough in vivo investigations to understand the importance of formulations. So yes, maybe in vivo studies really need to be done.

I guess the other thing I would say about in vitro is if we can dial back to the mid-90s, it would have been a good thing at that time to implement in vitro tests, even though maybe not everything was known. And I think a lot of people would probably say yes to that.

So sitting here today, yeah, there's a strong reason to develop in vitro alternatives, even in the absence of perfect information.

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DR. LIONBERGER: I think with that comment, we'll move on to our next topic, talking about the BCS class 3 waiver question. So I think we heard in the industry presentation concern that one reason why the generic industry doesn't use the BCS class 3 waiver option is the formulation differences.

I want to confirm with our industry colleagues that you think that's an accurate representation of the decision-making processes you go through when you consider whether to use a BCS waiver or not.

DR. SEO: I don't know about the generics scene with regards to Q1/Q2, but even on the new drug side, we have turned down requests for BCS class 3 because, primarily, one, the guidance is still in draft and, two, we're still building our knowledge base.

I think it's probably relative. We're being conservative until we know more. And then we can perhaps visit the idea of expanding beyond Q1/Q2. But for now, I mean, guidance just came out, so I

think we're still building our knowledge base there.

DR. AMIDON: I think probably the requirement for quantitative similarity, quantitative sameness is maybe too strict. But you need to do that the first time to get your feet on the ground. But then I think excipients desperately need a classification system.

I think IPEC made some proposals there. I think certain excipients are safe. Of course it's a dose-response curve. It's pharmacology, so I think it desperately needs a classification system for excipients.

DR. LIONBERGER: Yes. In terms of timing, right, now that the guidance is out for the Q1/Q2, that's sort of a settled issue. So the research frontier is what do we do next. So I think that's what is on the research agenda.

I want to Mehul can you give a little background on what the concerns were about differences in formulation for class 3?

DR. MEHTA: Yes. So actually, it's one of

the bullet points in M.J.'s slide. When we started devising our 2000 guidance in the BCS committee, this was around 2012, 2014. I think it was before even GDUFA was approved.

So at that time, when we looked at it internally, we did see examples, especially for very low permeable drugs like bisphosphonates. There was impact of excipients on bioequivalence outcomes for those products.

Then we have seen very few examples in literature, but academicians do pose those issues that excipients affect transporters. My personal take is, it is surfactant type excipients that largely do it, but that's sort of an unsettled issue.

The third thing, then, we looked at was other agencies' position on this. The EMA was out there in 2010 with their finalized view on this, and they are maybe even more conservative than us.

So in the absence of objective data, Siva mentioned something, and I would like to ask him a bit more about it. But in the absence of objective

data, if for example, in reality the excipients using IR and MR products have no impact on the permeability of APIs with the exception of [indiscernible].

So it would be wonderful if that was in the public domain, if it was analyzed and published. We would love to use that. But short of objective data, which we didn't have at that time, we had to start with that position. Since then, Jim has been working on the project for us, which was finally concluded and nice results there. So it does identify maybe like 10 excipients that don't affect total prototype class 3 products. But again, that is still being debated in the literature somewhat.

That was the real reason we started the position. I think, personally, there is room for growth very rapidly. Ethan is working on something internally right now, and I don't know if we'll have time to talk about it.

But lastly, we are dealing with the same issue with ICH also. This is one of the important issues that we want to resolve. And I think PhRMA

is working very vigorously on this issue, I think, along with IPEC folks.

So we have hopes of identifying excipients maybe on the lines of what Gordon was hanging up, classes of excipients where it'd be nice to have a no-problem excipient list where we know enough about them.

So that's a long answer, but the reason why we started that position -- and in my opinion, there is hope for very rapid improvement there. Internal work is going on, and I think at ICH, a lot of us are working on this same issue, and of course in personal academia, it is very useful.

DR. LIONBERGER: Jim?

DR. POLLI: Yes. Mehul mentioned a study that we did, actually a series of studies that we did, resulting in a publication maybe one or two years ago involving 14 common excipients. This was FDA funded, so it was very collaborative in terms of the design of the experiments, selection of the excipients, these common excipients.

The result was, for 12 of them, there was

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

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

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

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

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

DR. LIONBERGER: Charlie?

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

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

DR. LIONBERGER: I think the question on the

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

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

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

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ingredients are.

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

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

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

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such as the elderly or in children, given their potential difference in pathophysiology such as altered pH or gastric motility, and to what extent does this change the benefit-risk profile for excipients. So for example, HPMC, given that it's a pH-dependent solubility profile.

DR. LIONBERGER: Aloka?

DR. SRINIVASAN: I'd like to just bring up an interesting issue. I think, Mehul, I had talked to you about this some time back. When you are talking of Q1/Q2, I do remember when in FDA we had an issue with locally-acting tablets which worked locally. The innovator went and said just starch in the label, however, we internally knew what kind of starch was being used. When somebody uses corn starch versus pregelatinized starch, everything changes.

So here, I can understand where I was. I could not tell them, guys, do not use pregelatinized, use cornstarch. So now we are going into this -- like there are many vegetables, choose one of them, et cetera, et cetera.

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I think this is something FDA might face when you talk about Q1/Q2, and you will need to understand, like, can change -- just an example, pregelatinized versus cornstarch, would it make a difference? I think it would, but every product there will be a struggle there. So that's something we need to keep in mind about this.

About the abuse deterrence, changing topic there, it's something that always haunts me. What if an innovator is abuse deterrent by the pathway AB, but a generic can make a product, which has an additional abuse deterrence? How is OGD going to deal with that?

That's something we need to understand. If they want, will there be a label change, and how will the science support it and everything. I just wanted to bring this up, just food for thought, probably.

DR. LIONBERGER: Let's move on to our next topic. So I formulated the question here, talking about using integrating predictive dissolution methods, PBPK and PK/PD modeling for decision about

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generic drug bioequivalence standards.

So I think we heard from the industry perspective that the point that's most painful to the generic industry is when we make these decisions later, so it impinges in the development or even the review timeline.

So I'd like to ask the panel, are there ways that we can use these tools to make decisions specifically about partial AUC, different bioequivalence standards, or different bioequivalence expectations for various things that appear in the label or are needed to ensure therapeutic equivalence earlier.

So just broadly as that topic first to say, looking for that early decision point.

DR. MEHTA: Obviously, this is a topic of great interest for me on the new drug side and Ethan and others and Dale on the generic drug side. But we need to start thinking about these issues at the time of approval of new drugs. If there are going to be specific issues to worry about in terms of bioequivalence issues of this innovator products

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post-approval, they should be held to the same standard as OGD ANDA drugs.

So the knowledge base that needs to developed for identifying these issues and how to resolve them needs to be put together at the NDA stage. And then as now, we are working more collaboratively between new drugs, generic drugs through an NTI working group or other mechanisms.

That's the best way of, sharing information to the OGD colleagues, what's being done at the new drug stage. Then we can pass down that knowledge in time for OGD to prepare their product-specific guidances that are most informed.

DR. SEO: To add to that, we've had instances where we've done PBPK modeling essentially in the new drug space. The difficulty is when we try to apply the framework of that model to a generic drug, the legality of how much of that model can be shared, because not all of the information can transpose between applications.

So after we strip away from our NDA model the things that are proprietary, essentially,

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there's not much usable model left. In some instances, there are when the model is built on completely public information, available information. But for us, that has been the difficulty in implementing PBPK at the application stage for generic.

The other part of that is when we've requested that information in the ANDA, we often get a lot of pushback, and obviously so, because during the time of application, it's kind of late in the game to all of a sudden try to model something, especially if you know the agency is doing that.

The difficulty on the GDUFA and ANDA side also is currently we don't have, except for the PSRs, a paradigm to initiate those conversations with you guys early in terms of you should try this, modeling a simulation, this is how you should go about doing it, these are the kinds of things we expect, where in GDUFA, we have so many avenues to have those discussions early.

So that's been a real challenge for us, and

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we've been messaging it forever in terms of try this out, try PBPK, try modeling the simulation, especially in the quality realm. But it is a challenge, but I reiterate that message here, I guess.

DR. AMIDON: Paul, yes. We all appreciate the public policy issues you have to deal with because that's public policy. But I'll go back to what Mehul was saying. I think you're touching on what I think is maybe the biggest soft spot in our industry because the commercial innovator product has to be bioequivalent to the phase 3 product. Right? Because the phase 3 product is the only one we have data for. Everything on the market has to be generic, including the innovator, to the phase 3 tested product.

The dissolution standard on the phase 3 product should be our pivotal standard if we had a good dissolution test.

DR. MEHTA: Just to clarify what I was saying, my comments were mostly restricted to if we need to worry about additional BE criteria for a

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specific product like partial AUCs, things of that nature. And that's what we have done for, for example, methylphenidate products, Ambien CR.

We had a lot of good data at the NDA stage for us to evaluate those issues properly. So we had to worry about that at the NDA stage. And then we brought it over, and our OGD colleagues worked further on those approaches.

When we worked on it, of course, all very extensive and sophisticated modeling approaches were used, and Joga was one of the main architects of that. So there is definitely a lot of scope and potential for it. We just need to continue to work better on it and more collaboratively.

DR. LIONBERGER: Joga?

DR. STIER: Sorry, Joga. Yes, Joga was heavily involved in that. I agree with most of the comments said already that for the methylphenidate products and the Ambien, which I believe there was an advisory committee at the time a few years back, that was really an evolution.

Part of that was a combination of, one, I

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think having a long history of understanding that there were strong PK/PD relationships for the API, but I think the new layer that got added on is there's kind of a delayed or lag time, if you will, between new formulation technology that's potentially used on the innovator side, and then those products, when they come off patents, generics are trying to match those characteristics.

I think some of the approved labeling for some of the products that we're talking about, where that's actually incorporated in the language of labeling, that the product is designed in a particular way to deliver drug for which there is a strong PK/PD link. And the way in which it's delivered is very important to the therapeutic efficacy of that product.

So that led to this evolution in thinking on these types of products, in a timely way I think. And I think that, although it hasn't been I guess ratified, if that's the right word, but at least in the drafts of the GDUFA 2 commitment letter, I think that in a sense will be driving a lot of

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

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

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

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

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So it doesn't really get us out of the expensive, onerous doing real human or other types of data. It just enhances that and enhances our understanding.

I also think that a lot of the knowledge that we would put into a model or put into understanding, for example, our knowledge of excipients, really, I'm almost amazed that every so often, we find out something really brand new to us, anyway, about some excipient that we've used for 30 or 40 years.

The example that comes to mind is sorbitol or other alcohol sugars. We often assumed that in the regs, which were written a long time ago, if you have a solution, a solution dosage form, everything is in solution, excipients, the active. What could go wrong? We should just waive that. And then we discovered much later in the game that alcohol sugars for certain types of products really affect them, even though they're in solution already.

That was a very BCS type of finding. We

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didn't understand it way back when those regs were written, but now with the BCS data and the understanding that that brings us, we now kind of understand what's going on with that.

But there are probably other things lurking out there where we assume we know quite a lot and we don't really know as much as we think. Modeling, and real studies, and real biopharmaceutic studies will help us understand that, but I don't think we're still at that perfect level of knowledge about even inactive ingredients, and not only the inactive ingredients in isolation, but how they interact both with each other and the drug substance because something could be good for the first 100 products you use it in. But you use that 101 product with another excipient, and they both interact in some way with the drug, and all of a sudden, all that I thought I knew is not quite as accurate as I thought it was.

So I think we should use modeling as a tool, but understand that it's not like the magic bullet that's going to solve all our problems.

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DR. LIONBERGER: Lucy, and then Raj?

DR. FANG: We heard from our industry colleagues today that we really want FDA to share alternative BE recommendations and the prospect proactively and also in a timely manner. So how can we get there?

So we heard from Mehul, we can enhance OGD/OND collaboration. We gain better understanding from the new drug development. The other way is that we can feel the gaps in our knowledge base, and that's where we are with the regulatory science program.

So Joga, you mentioned that the models for the new drug and generic drugs could be very different, so I would like to hear more thoughts from you, other research needs in this regard.

DR. GOBBURU: If you think about this problem from the clinical end all the way to the product, the excipients and such, that's how I would think it would be most meaningful. First, we need to find an endpoint. It doesn't need to -- it probably cannot be in most cases. It doesn't need

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to be an endpoint based on which the drug is approved. It should be an endpoint that means something to the efficacy or the pharmacological activity more so, not just efficacy, but pharmacological activity.

So you need to find one or two, preferably one, biomarker endpoint which is sensitive enough to the changes in concentrations. You don't want to have an endpoint which is cumulative, like survival, which probably doesn't move even if you half the dose or double the dose probably.

DR. FANG: So you want more from an endpoint perspective.

DR. GOBBURU: No. That's one big change from the NDA BLA views, because that's all focused on approval endpoints, mostly.

DR. FANG: So the question I would like to ask is from a broader perspective, from a technique perspective.

DR. GOBBURU: I see. We talk about this, and there are technologies and expertise to do each one of them separately, but I have never seen

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

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

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

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

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

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

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

Given its importance, I want to allocate

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

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

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

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

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

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

A physiologically based model can help build

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

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

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

Of note, all of the decisions that a PBPK

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model have contributed has a direct impact on the product approvability.

In the following slide, I will talk about quantitative clinical pharmacology and its impact in the generic drug development and review.

The most commonly used toolkit available in quantitative pharmacology starts from new drugs, and they can be shared between new drug and generic drug development. For example, PK/PD modeling for new drug development is also the key to advising BE study design, sensitivity of PD endpoints-based BE assessment.

Population PK can be used for model-based BE assessment for drugs with sparse PK sampling. The equivalent part of a clinical trial simulation for generic drug development is virtual BE study.

What is a virtual BE study? It's the use of a model to compare test and reference formulations based on the computer simulations. The model must have a formulation variable that can be adjusted to represent a difference between test and reference. The model generates a population for BE study and

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compares the test and reference product in that formulation. We can simulate many studies to estimate the probability of success and failure, which we usually call the power assessment.

Quantitative clinical pharmacology is an established and useful toolset for solid oral products and applications. The key question and challenge now is can we develop a further thought on model-based drug development for locally-acting and complex products?

This slide, I've shown earlier. It shows the areas that quantitative clinical pharmacology has contributed. The red color indicates the application areas that are closely related to complex or locally-acting product.

For locally-acting product, we always have an interest in further abbreviating the program for regulatory science research for model-based BE assessment, and using appropriate PD endpoints or biomarker which can be more sensitive to establish BE and more sensitive methodologies for clinical endpoint evaluation and assessment.

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For complex dosage form such as long-acting injectables, models can be used to establish the new metrics for BE assessment. For other applications, pharmacometric tools have been routinely used for NTI drug identification, classification, and a PK metrics determination.

Applications of quantitative clinical pharmacology in the realm of generic drug review ranges from across PK metrics determination BE study design, clinical endpoint evaluation, and in vitro BE assessment.

This table summarizes what we have done in the calendar year 2016. Here, I want to say that a good modeler not only will have high technical expertise, they are also good philosophers. They are strategists. Before we do a model, we need to think based on the data, based on the information, based on the experimental result, in vivo/in vitro studies, how do we want analysis, analyze data, and what tool should we use, and what conclusions can be safely drawn from the toolset.

I'm very glad that the division has

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assembled the key skillset and a bunch of brilliant scientists in this area. Not only for PBPK, PK/PD, we are also actively thinking of development models that can be used to evaluate health outcomes and big data. With the advancements of new technology, information or data explosion is happening everywhere. Motion learning is one of the most popular techniques that enables data-driven decisions into a process.

There's no difference from FDA. Currently, the efforts are many within FDA. Big data models have been exploited in the areas including but not limited to the following: to predict work load, to prioritize scientific research needs, identify areas for healthcare cost reduction, and opportunities for regulatory communications.

Under the GDUFA regulatory science program, around 30 grants and contracts have been initiated that are closely related to quantitative methods and modeling. They mainly are partially fall into subject areas such as further BE investigations, identification of new BE metrics, PBPK models for

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systemic and locally-acting products, model-based BE assessment based on PK or PD endpoints, postmarket evaluation, and NTI classification.

These two tables summarize the 30 or so grants and contracts. Given the time, I cannot go through them one by one. Every one of these grants and contracts are of high importance to inform our internal regulatory decision-making.

Today, we should be more focused on the further research needs to enhance the program. We continue to face regulatory challenges from the area of BE assessment for complex and locally-acting product. Recent advancements in science have created several innovative pathways for BE of locally-acting products in addition to clinical endpoint BE studies.

Specifically in combination with a broad spectrum of in vitro/ in vivo testings, quantitative methods and modeling is one of the key toolsets. Model-based guidance development for complex and locally-acting product will ensure timely availability of high quality and affordable

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generics for patients.

The current research priorities from FDA perspective includes the following: develop PBPK models for complex routes of delivery, including nasal, inhalation, dermal, ophthalmic where there is limitations to generic competition; use quantitative pharmacology and bioequivalence trial simulation to optimize BE studies for complex products; leverage big data for decisions related to generic drugs.

For each of the priorities, the key questions for input from the panel are opportunities to use modeling to inform regulatory decision-making in both pre-ANDA and the review stages and gaps that need to be closed for quantitative methods to provide evidentiary support for drug approval especially for locally-acting and complex products.

With that, I would like to thank everyone, thank the panel and the audience, and looking forward for more constructive discussion in the following session.

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DR. CHOI: Our next speaker is Dr. Amitava Mitra from Sandoz, who will provide the industry perspective on generic drug research needs.

Presentation – Amitava Mitra

DR. MITRA: Thank you, Stephanie.

Thank you, all, for being here and for inviting me today. I'm going to talk about or give my opinion on the application of physiologically-based PK modeling in generic drug research. Just a disclaimer, it's my opinion, so hold me responsible if you don't agree with anything.

This is a brief outline. I will just very briefly go through some introductions. A lot of it has already been covered in the previous presentations and Liang, so I'll not belabor that much.

I'm going to focus primarily on virtual bioequivalence and where I think there is a lot of room where this could be applied in generic drug research particularly. I'll give two examples where we have had success on virtual BE, one CR example, and immediate-release example, and then

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conclude, and a slide on future use.

So before I get into modeling and simulation and talk about that, modeling, as we all know, is a pretty broad field, and terms are used interchangeably. So I just wanted to make sure that the audience understands what I'm going to talk about today.

So what I'm going to focus on today is particularly physiologically based oral absorption modeling. We are not talking about DDI. I use PBPK here, but it's not really full PBPK. We're going to focus mostly on oral absorption model and try to answer CMC questions particularly. So that's the focus of my talk here.

This schematic is just to show that the kind of information that we need to build these models from the ground up, you need formulation, compound information, some kind of a PK input, either compartmental or PBPK if that's what you're after. And then of course the GI physiology is very, very important, and I'm going to talk a little bit more on that as I talk about virtual BE.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The other thing to note here, and I

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

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

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

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

see the CIs there. Some of them are not even close to what the observed data was. So there are some things that need to be obviously a lot more room to improve there.

Finally, here is the "pivotal batch" and the RLD. Again, the same thing was done. I'm just showing you an example of the fasted state here. You can create almost like a heat map. Run this virtual trial and see how many times of these do you fail and how many times do you pass.

In this case, it shows there are 3 out of 10 chances it will fail on Cmax and 2 out of 10 chances fail on Cmax. But it's probably a risk worth taking, again, depending on the situation of course; and then here, the model predictions and the observed bioequivalence data. And in this case, the model seemed to have done pretty well. At least, it's predicted it's going to be bioequivalent.

So that's an example of a controlled-release formulation, and here is an example of case 2 of an immediate-release product. This is etoricoxib, a

BCS class 2 molecule, weak base, fairly highly soluble, a typical weak base, very high solubility, at low pH, and the solubility drops as the pH increases.

Now, in this particular case, the struggle that we faced was which dissolution is the most predictive of bioequivalence? And the situation that we were in, it was in a SUPAC. There was a manufacturing site change, and multimedia dissolution was done. And at 4 and a half and 6.8, it was not F2. So obviously, we were stuck in a BE situation here that we wanted to avoid.

Another thing to note here is etoricoxib, even though it's a weak base, there is data that as it goes from the stomach to the small intestine, there is not much precipitation happening there. So A, it's completely soluble in stomach, and B, as it transits from stomach to small intestine, there is not much precipitation.

So we were arguing that this high-pH dissolution was overly discriminating. It is not relevant from a bioperformance perspective. And we

set about proving that through modeling. So we obviously did a lot of work just building the model against all available phase 1 data, different phase 2 PK data, food effect, et cetera, and I show you some example here of the model performance at the high dose.

Again, we ran some virtual trials, and what this model showed was that if we use the pH 4 and a half and 6.8 dissolution, it will predict that it will not be bioequivalent, although at pH 2, it will be bioequivalent.

Again the argument that we were putting was that 4 and a half and 6.8 pH is not biorelevant. It is not biorelevant in this particular case. Then nevertheless, we had to run the BE study, and the BE study came out to be -- even with those F2 differences, the batches were still bioequivalent. And the GMRs were in fact very, very tight.

So this is an example where, again, in this particular case, pH 2 dissolution was the most biorelevant, so this is an example of where understanding what dissolution input is needed is

pretty key for these bioequivalence predictions, of course, otherwise, you can be completely misled.

So with that, just to conclude -- I think I have two more minutes -- overall, the experience of these models, specifically in the CMC area, has been pretty robust, both in industry and in the regulatory agency, although there's a tremendous potential of these models in generic drug development, specifically in virtual bioequivalence setting.

I completely agree with Paul's statement at the last panel that I think as a generic industry, we need to be utilizing these models more. I think there's a lot these models can help us with. I did not talk at all about complex drug products, but some things like long-acting injectables, again, the models are being developed, so there's a lot that can be utilized in that arena, too.

Finally, for future use, again, I took this slide, and Rob was kind enough to let me use his slide from the last AAPS. I think it pretty much summarizes my thoughts to expanding BCS class. We

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had a lot of discussion about BCS class 3 waivers. I think these models can be used a lot in those cases if you are not Q1/Q2.

Again, in specific cases, even in BCS class 2, I showed an example of etoricoxib. So even specific cases in BCS class 2, I think with enough work done, these models can be used.

Fed, I personally think we do way too many fed BE studies, and some of them are pretty low-hanging fruit that could be waived, and there are others. Hopefully, we'll get to that during our panel discussion. So with that, I will just end my presentation and thank you.

(Applause.)

Public Comment Period

DR. CHOI: We will now begin the public comment period for this session. Our first presenter is Dr. Yu Feng from Oklahoma State University.

DR. FENG: Good afternoon. Thank you very much for giving me this opportunity to talk about our research. So this talk is about testing the

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new targeted pulmonary drug delivery method using computational fluid dynamics, fluid particle dynamics method.

The motivation is straightforward, as discussed by a lot of people today. Using modeling saves time and money, and it's not non-invasive. Also, using the CFPD method, it can provide high-resolution results, so it can provide more information to generate the physical insights.

Talking about the targeting, what we want to achieve is to reduce the side effect, to enhance the therapeutic outcomes. In that case, we can control the particle trajectory by only manipulating their release method.

I'll just skip the governing equations. So conventional pulmonary drug delivery, when we inhale the drugs, it can spread everywhere. What we want to control the release. For example, in this slide, we want to release the particles solely in the yellow region, and most of the particles will end up in the left upper lobe.

Another example is this one. If we release

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the particles in the green zone, most of the particles will reach the right lower lobe. So in this case, we can just manipulate the release position of the particles, and we can achieve this lobe-specific drug delivery.

So talking about this simulation, it is only visible for that specific long-area geometries. What we want to do to enhance the capability of this simulation framework is to want to make this work for at least the population.

So there are three works, we think, that are necessary to further extend our simulation. The first thing is about intersubject variability study. That means that we want to have this CFPD simulation with arrow bars, so we want to build up a virtual population study, so in that case, it can be a test whether it's feasible for the population or somehow it can be restricted to a certain small cohort.

The second thing we want to do is try to extend the capability of the simulation. The endpoint of the drug is not a deposition, but it's

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the other deposition dynamics. We want to see the translocation of these drugs, so we want to combine the CFPD model and the PBPK model.

A third thing is we want to generate a fast and accurate tool to provide us with a precise treatment plan, meaning that we have a patient coming in, They have a specific disease, and based on all the inputs they gave us, we can just directly give them an optimized drug formulation and optimized drug delivery method.

It's all about the big data and machine learning. The data we viewed is based on our simulation results using a CFD model. So this is our virtual human, version 1, so this is something we want to use for the subject variability study, and this is all the geometries we have, upper airways and long-airway geometry. So we can combine different options, and we can generate a virtual population.

The last thing is all about this multi-scale modeling. So yes, thank you very much.

(Applause.)

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DR. CHOI: The next speaker is Dr. Scott Mosley from the University of Florida.

DR. MOSLEY: Hi. Thank you for the opportunity to share our thoughts with you today. I'm briefly going to explain -- really, this is my only slide. It's just the title of our current FDA-funded project, Open-Labeled Pharmacokinetic and Pharmacodynamic Studies in Metoprolol ER.

This is briefly one of the recommended studies by FDA specific from metoprolol succinate formulations. If you don't get the waiver, this is what they would suggest you do to show bioequivalence.

So we're conducting this, just normal PK and the PD part, a 24-hour ambulatory blood pressure, Holter monitor for heart rate, and a smart pill that they ingest, which reports pH, pressure, temperature, and time.

I don't have any data to show because it's still ongoing, but just clinical observations, I'm working as the research pharmacist on the project. We have noticed some things that are generating our

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next round of grant writing and ideas to share.

So we've noticed there are similar blood pressures between the formulations, which is expected, but we're noticing possible differences in heart rate. So something to focus on, not necessarily blood pressure anymore, is beta blockers are no longer first-line per JNCA [ph] a couple of years ago, but they are still first-line in heart failure.

Another is the emerging data on these inactive ingredients, in particular HPMC, hydroxypropyl methylcellulose or hypromellose. And it may have an influence on metoprolol ER release characteristics, as shown by some of this PBPK modeling.

With the heart failure model, we feel like that would be more important moving forward as the metoprolol ER product is superior to the IR product. This is a special situation where that has been shown, and it's due to the release characteristics of the drug, which are very important, that you may not see when looking at it

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in vitro. But in vivo, it changes the heart rate variability.

So using those ideas, we have mainly two suggestions for possible research, one being this marriage of the translational research between PBPK modeling findings with in vitro and in vivo being the clinical trials. So we could focus right now on this HPNC and see if these PK models are predictive of what we see in vivo and in our clinical setting. And that's particular for metoprolol ER.

The second would be to still keep an eye on the influence of clinical efficacy in ER formulations rather than give the waiver, focus on this type of situation, where ER products are superior to the IR products, like the case of metoprolol in heart failure. Thank you.

(Applause.)

DR. CHOI: Our last presenter is Dr. Kenneth Morris from Long Island University and also representing NIPTE.

DR. MORRIS: Thank you. I'm batting

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clean-up again. Today, I just wanted to talk real briefly about a proposal that's currently part of EO1 in front of FDA called New Prior Knowledge. And basically, the idea is that drugs that are coming off patent now, that might be developed as generics, were studied, and studied years ago with techniques that may have advanced or may have changed.

Also, there are drugs that already off-patent that are not being developed as generics that should be. Janet Woodcock testified that there were some 1800 such compounds, and some of them may not be developed because of financial issues, but many of them because of technical issues.

So what's really needed is a public knowledge base to provide information for all contenders to get this backlog of compounds started down the path, as well as to reduce cycle times and to take care of the out-of-date characterization.

The new prior knowledge is sort of an acronym -- or not an acronym, but NPK is the

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acronym for New Prior Knowledge that basically says that there are compounds for which the information needs to be generated now so that companies unable to marshal the resources against the projects can have access to it. It seems pretty obvious to us, of course.

So the end result of that I've outlined here; I won't go through this slide. But the end result of that could be something that would be something like NIPTE monographs, if you will, that would be generated by the collaboration of the 17 departments, and schools, and different universities working on these projects or, and/or I should say, knowledge bases that will be available to companies that are wishing to develop such compounds.

A recent poll that Ajaz Hussain just shared with us is that 90 percent of Americans, Republicans, Democrats, Independents, Anarchists all favor measures to promote generic product development. So this is not partisan. It's not controversial. It just needs to be done.

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As I said, this is part of EO1 that, actually, Steve Byrn is leading that has been submitted and is in front of FDA. You can think of New Prior Knowledge as a Lexus-certified pre-owned car. So it's not that it's not vetted. It's vetted very well, but it's information in a context that wouldn't have otherwise been available. Thank you.

(Applause.)

Panel Discussion

DR. CHOI: I would like to thank all the speakers and all those who have presented comments during the public comment period. We will now be starting our panel discussion, and I just wanted to remind all the panel members to please speak closely into the microphone, and also for any members of the audience who will be participating in the panel discussion also to speak closely into the microphone as well as announcing your name and your affiliation before you present your comment.

Before we begin, I'd like to now ask each of the panel members to state their name and

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affiliation, starting with Dr. Ethan Stier.

DR. STIER: Hi. My name is Dr. Ethan Stier. I'm the director of the Division of Bioequivalence II, Office of Bioequivalence, Office of Generic Drugs.

DR. AU: I'm Jessie Au. I was a professor of pharmaceutics at Ohio State for 30 years, and I traded that job for four. So I have three jobs in academia, where I spend about 60 percent of my time to develop a new program, a system-based modeling approach to help drug development. This includes two endowed-chair professorships at two universities. The rest of the time, I'm a CSO of a clinical-stage biotech.

DR. CONNOR: I'm Dale Connor, director, Office of Bioequivalence in OGD in CDER.

MR. DiLIBERTI: Charlie DiLiberti, an independent consultant with Montclair Bioequivalence Services.

DR. GROSSER: Stella Grosser. I'm with the Office of Biostatistics in the Office of Translational Sciences in CDER, FDA. I'm a

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division director for DB-VIII, which is the group of statisticians that support OGD.

DR. HOCHHAUS: I'm Guenther Hochhaus with the University of Florida.

DR. MITRA: Amitava Mitra, clinical development, Sandoz.

DR. POLLI: James Polli, University of Maryland.

DR. ZHAO: Liang Zhao, division director, Quantitative Methods and Modeling, Office of Research and Standards, OGD.

DR. TSANG: Yu Chang Tsang, chief scientific officer in biopharmaceutics and biostatistics at Apobiologix, division of Apotex.

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

DR. ZHAO: Ping Zhao, pharmacometrics, Office of Clinical Pharmacology, FDA.

DR. LIONBERGER: Rob Lionberger, director, Office of Research and Standards, OGD.

DR. SEO: Paul Seo, director of Division of

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Biopharmaceutics, Office of New Drug Products, Office of Pharmaceutical Quality.

DR. CHOI: Thank you. The first priority area that we would like to receive input relates to the development of PBPK models for complex routes of delivery such as nasal, inhalation, dermal, and ophthalmic routes where there are limitations to generic competition.

I'd like to ask Dr. Jessie Au to start us off on providing comments regarding challenges as well as new approaches or strategies in PBPK modeling for these locally-acting products.

DR. AU: Yes. I was listening all day, and I was thinking about how some of our own work and the lessons that we have learned would apply here, especially for the locally-acting drugs, and also looking forward to the future, where you're going to have lots of new cancer drugs that's coming off patent because in the oncology field, there have been a large number of drugs approved in the last 10 or 15 years.

So I think all those point to one thing,

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that we may want to look into supplementing PBPK. So in my entire career, I've been developing drugs for locally acting, so mainly for organ-confined diseases in bladder cancer, prostate cancer, and now peritoneal cancer. So in our case, we actually want not to leave the locally-acting site. So we're dealing with the same problem you are faced with.

Now, the other thing we also do in cancer is a little bit more complicated than other organs because cancer is not normal. It's not natural. Its development is chaotic. The blood circulation is very chaotic. There's a lot of spatial heterogeneity.

So how did I extrapolate that to the question you asked about locally-acting drugs? One thing we had to deal with in our case was to be able to predict from compartments where we can sample, and now to be able to predict the concentration of drug and time profile as a function of space, so the distance it traveled, how does a drug travel from point A to point B? What

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are the chaotic systems we encounter? What is the extracellular matrix we have to deal with?

So at the end, instead of using a probabilistic approach like PBPK, we actually are using a deterministic approach. So we are pinpointing a point in the site where you want to know where the concentration is.

I think that type of approach, which is loosely called multi-scale models, can apply in locally-acting agents, And it also would apply in cancer drugs that you're going to be dealing with, because a lot of those are large molecules. The transfer's going to be very difficult to deal with. You cannot take one generic versus the innovative drug. It's more complicated than small molecules.

I hope that's clear.

DR. CHOI: Any other comments from the panel?

DR. ZHAO: I just want to follow up with Dr. Au's comment. You mentioned a sample drug for PK measurement from accessible parts. So does that refers to the action set or some other site that is

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maybe a surrogate organ for the --

DR. AU: Very good question. Thank you, because this is hard to explain in just a few sentences. So I'll give I think now the best example that I have. I'm sorry. I back up. There's a better example, work that I had done about 30 years ago in bladder cancer, where we basically predicted concentration at tumor, where we don't even know here they are. But we predicted concentration, we synthesized the phase 3 protocol, and we did a phase 3 trial. And now prediction came out right on the money.

So that gave us the confidence that you can actually predict a concentration in spatial, rather than just by time. So that's one example.

The other example, I am about to do a clinical trial, so I can tell you soon whether it will work. This one is a little bit more complicated. This is peritoneal cancer, where we put a drug in the peritoneal fluid.

So we can tap the fluid; we can measure that. We can also measure the blood concentration.

So by having the two compartments on two sides, I can predict what's in the middle. And of course, the more constraints you put on the model, the more likely your model is going to be correct. So in animals, we've proved we can predict the concentration as the drug enters the tumor as a function of distance, so that space on sampling the peritoneal cavity and the blood.

Now, the bladder cancer situation is actually similar. We just sampled the urine because that's the most easy one. The drug never enters the blood, just like what you have in your locally-acting drug situation.

DR. CHOI: Any other thoughts on this priority area?

DR. POLLI: Yes. Just maybe point out the obvious. Dr. Zhao and Dr. Mitra, the two speakers were incredibly harmonious on the issue of, yes, this seem to be very, very important.

In terms of just my own background as an academic, I would just add that it's extremely difficult to understand how these more complex

products work, even remotely, without actually someone really going out of their way and studying it. So to me, this is just an obvious big priority.

DR. LIONBERGER: One thing we heard in the morning session, and where I think it's an important application of these, is that for a certain subclass of these locally-acting products, you can measure systemic PK levels if you think that that's going to be something you wanted, and then say, well what does that observation tell me about the local concentrations?

I think a model that captures your understanding can really be very useful for telling about -- like, for example, if I look after inhalation results, I can say, is there any possibility that looking at the PK profile tells me where in the lung it went, depending on how I know that drug is absorbed or looking at a drug that passes through the different layers of the skin.

So I think there's opportunities there in certain situations to use these models to link to

interpreting different types of information that we see, that maybe are alternatives to these insensitive clinical studies.

DR. HOCHHAUS: In the area of inhalation, my personal case, modeling has helped me to understand just much, much better what is going on or what might be important. And it also has helped me to maybe identify parameters that will mirror potential differences in the lung.

As you said, can systemic PK be a mirror for potential differences at the site of action? And for me, modeling has helped that quite a bit, and you can then also in the next step ask questions, if there is a certain difference maybe in vitro properties, what kind of effect would that have on the situation within the target organ and how would that then further be shown downstream.

So from that point of view, modeling has helped me quite a bit and maybe also to find arguments to find to say, yes, certain parameters that we're going to monitor will potentially reflect differences at the site of action.

DR. LIONBERGER: Yes. I mean, another example that you saw is what Bob Bellantone has talked about, but you put an ophthalmic drop and it's reduced and cleared down to a thin film.

For me, that's a problem in fluid mechanics and computational fluid modeling to say how fast the drops stay there. And that's a testable prediction. You can look at the drop and see how thick your film is. So if you generate testable predictions, it really helps understand how formulations distribute across some of the local routes as well.

So it's not just the PK aspects of modeling, it's really both the formulations and the physiology aspects of these types of routes. And they're complicated. You look at the pictures we saw of the lung generation model. We funded research in that area as well to build better models of generation after generation of lung branching to predict where drugs get deposited as well.

So it's more than just the PK

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interpretation. There's lots of the physiology and formulation interaction you have to capture here. So here it's a research frontier. It's much less established than the oral routes of administration.

DR. AU: I think the CFD, the computational fluid dynamics, are especially useful when you start doing multi-scale models, when you can actually take one scale and separate it into different compartments, and then start feeding whatever fluid dynamics you want to do.

So I think what Rob said there, I think that's something we in pharmaceutics have not used as much. And I think Stella mentioned at one point that this is where we reach out to chemical engineers and learn from them, and then help us in this direction.

DR. CHOI: Thank you. I will move us to the next priority area, which relates to the use of quantitative pharmacology and bioequivalence trial simulation to optimize bioequivalent studies for complex drug products.

I'd like to ask Dr. Yu Chang Tsang to

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comment on this topic and the opportunities available to use modeling to inform regulatory decision-making during the generic drug review process.

DR. TSANG: Thank you. This morning, we heard that there were very few generic products approved for complex drugs, and they have a good reason for that, because the requirements are very stringent. And I'm very happy to hear that the FDA is open for a different means of demonstrating bioequivalence because I think this could be very important to generic industry in the following main areas.

We heard that, for certain complex drug products, we can use in vitro testing in some situations with also PK bioequivalence to assure for better equivalence, but for certain complex drug products where clinical endpoint studies are required, I think modeling and simulation can be very useful for helping to reduce variability, the high variability that can be observed in clinical endpoint studies.

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We heard products this morning like acyclovir cream, cyclosporine products, ophthalmic products. Their products have very marginal efficacy, so if one is to design a clinical endpoint study on those drug products, it can be very challenging with respect to the definition of the equivalence criteria because those products have so marginal efficacy.

If you try to apply the traditional 80 to 125 percent equivalence margin, one will find their sample size can be extremely, extremely large. It could be in the hundreds of thousands of patients. And that can really create a hardship for generic companies to conduct a clinical endpoint study in order to demonstrate equivalence to the innovator product.

In situations where the variability of clinical endpoint studies is associated with the design, perhaps we can also use simulation and modeling to develop a design that can reduce variability of the study. For example, for inhaled corticosteroids, the proposed design is based on a

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parallel design.

Perhaps we can consider looking at using a crossover design. Can we use simulation and modeling to allow us to establish a design based on a crossover design such that variability associated with the endpoint can be reduced. As you know, currently, with the parallel design, again, we need hundreds of subjects to demonstrate equivalence for FEV1 for inhaled corticosteroids. So I think that is another area perhaps that modeling and simulation can be used.

For other complex stuff like the long-acting injectables, perhaps we can also use modeling to determine what truncated area can be used instead of doing a very, very, very long study. With a truncated area, we can shorten the study. And again, with the study being shortened, we can apply a crossover design to reduce variability. So that's another area where perhaps simulation and modeling can be very useful.

We talk about NTI drugs. Currently, the FDA guidance requires the use of reference scaling for

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bioequivalence of NTI drugs. And the reference scaling needs to be applied even when the variability of the reference product is very low. The question is, when the intrasubject variability is as low as 5 percent, the reference scale criteria can be very, very narrow.

When different lots of the reference product can differ in their drug content by up to 5 percent, is it necessary, is it perhaps a necessary stringent to apply the reference scaling down to that level when the lot-to-lot variation of the reference product can be as high as 5 percent.

Perhaps we can use modeling and simulation to assess the developments of the application of reference scaling when the variability is so low. Thank you.

DR. CHOI: Any other comments, Jim?

DR. ZHAO: Just quickly in response to Yu Chang's comment, I think it's a really good comment. And I just want to briefly say that we welcome industries, too, if you have good thinking of whether applying innovative approach or

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quantitative methodologies in the drug development program, you are welcome to include that in the package in the pre-ANDA interactions or even in the application itself. I think there is a broad array spectrum of modeling impact we can make in making safe but effective generic product with the public.

But having said that, our general expectation, as also elaborated by Dr. Dale O'Connor from the last panel discussion that the model needs to be qualified, verified for the purpose of the use. Depending on the application purpose, you may have a high barrier for qualification or a low barrier for qualification.

It also relates back to the comment Dr. Raw raised at the very beginning saying if we have some observations that can be used to validate the model, then that give regulatory agency very high confidence in accepting the proposal.

We are modelers. We are also strategists. We really want to have decision-making, but with solid evidence. The model can be used to sometimes replace part of the clinical endpoint study, but it

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can be used to -- previously, you only analyzed data at a single time point, but if the longitudinal analysis can allow you to reduce the size of the trial, then we welcome all those ideas.

DR. CHOI: Jim?

DR. TSANG: I'm very glad there's an opening for that. I remember several years ago when we had to file control correspondence, it took years, years of waiting before we can hear any response from the FDA. So I'm very glad again to know that there is an opening for Pre ANDA discussion. I mean, that will certainly help the industry a lot.

But I think FDA is in the best position to use modeling, because you have access to data from the new drug side, which generic companies will not have. And to me, you are in the best position to look at modeling.

DR. CHOI: Jim, do you want to make your comment?

DR. POLLI: The same comment as far as impact, not so much relying on new drug data, though. But Dr. Zhao kindly sent me his slides

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ahead of time, and I'm just noticing the highlights of quantitative clinical pharmacology impacts. And it's just nice to know when it has been successfully used.

Also, in looking at this, I was thinking of what I heard in Dr. Amitava Mitra's talk. As a representative from I think a generic company, he seemed to really like the fact that you are advocating modeling. And what was going through my mind was he must have a hard time -- not necessarily him, but hard time convincing his administration that there's some value in modeling.

So I guess my main point is it's probably nice that you're promoting this because it really helps people make the case that, yes, there really are real examples, slide 18, where it could be helpful for a generic manufacturer.

DR. LIONBERGER: I'd like to ask the industry representatives a question. In this question, you're talking about, before you do it, especially these expensive large -- I'm thinking a clinical endpoint study or a long-acting

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

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

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

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

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

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

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

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

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think that, as Rob said, there is a missed opportunity there with regards to doing that modeling up front. Again, inevitably, there will be some kind of manufacturing change, or a site change, or maybe something even more disastrous than that, where you have a CRO that's in trouble, and everything at that site is now shut down.

Well, a lot of times, the first thing that's asked is, what data can we save? What's the quickest thing that's available, dissolution testing, some kind of in vitro release test? And if you have that model in place, that will answer some questions versus just immediately pulling everything off the shelf.

So I think there is some utility in putting that investment first; you got to pay to play kind of mentality. So I just wanted to address that as well. Thank you.

DR. AMIDON: I think we need to --

DR. CHOI: Could you state your name and affiliation?

DR. AMIDON: Gordon Amidon. I think we need

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to parse the term "model" a little more carefully. I think, often, the problem with the model is the input, the initial condition, not the actual structural model, although that needs to be refined to.

I think Amitava gave a very nice presentation. I agree with you completely. The USP dissolution methodology doesn't help you at all because it's not in vivo relevant. So if you got bad input, you're going to get bad output.

So I think it's maybe not the model that's the problem. It's the initial condition.

DR. CHOI: Guenther?

DR. HOCHHAUS: I just want to also stress what Dale said, that simulation alone will not be a substitute for bioequivalent studies, but it can be tremendously helpful, I think, in showing bioequivalence that can start from making the formulations/device; asking the question if I have certain geometric constellations, would that might eventually have an effect on the dose or the regions where it will be deposited if I am thinking

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still inhalation.

It can be very, very helpful in either identifying maybe alternative test methods, where you can just use clinical trial simulations and maybe show and convince people at the FDA, if we design that study in such a way, it will be much less expensive, we need less numbers, and the variability will be smaller.

The thing that's also very, very, very important in argumentation with the agency is if, for example, a question comes back, quite often you can answer those questions. If you have good models, you can answer those questions with models other than doing another study. And sometimes, it's successful, and sometimes, it's not. But sometimes it is. And I think modeling can help that tremendously.

DR. CHOI: Dale?

DR. CONNER: I'd like to just give a brief response to a comment that was made about eight people back, that FDA is in the best position because we kind of see all the data.

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There's some truth to that, but there are many people, or quite a few people at this table, not only FDA -- and FDA sees a certain view of the data. We see a lot of people's data, but it also is kind of filtered in a way. Now in ANDAs, we some failed studies. We see some extra studies that we never saw in the past.

But still, we don't see the studies where a company has made a formulation and it's just a total bust. They do this study, they get a lot of data, didn't work, they have to start again, and they go through. We never see that. So we're not fully informed of what changes or different strategies to design a product are successful and what are not.

Others at this table, namely the sponsors, see their own studies. And if you're a fairly large sponsor, you see probably quite a few. You're trying to develop multiple products over a number of years. You're commissioning studies. So you see it from a certain view, and you see some things probably the FDA doesn't.

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

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

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

Nobody has it all, nobody has all the

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

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

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

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

On the modeling issue, what Gordon said is

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

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

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

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

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

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

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

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

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

DR. CHOI: Thank you.

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

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

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

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

DR. CHOI: Thank you.

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

(Laughter.)

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

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

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

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

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

Closing Remarks – Kathleen Uhl

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

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

thanking industry.

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

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

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

move the issues. So I thank you guys for that.

The other thing is that there's a lot of other people that I need to thank here. I want to express my appreciation to everyone who attended today's workshop. The room was pretty full early in the day. We've had kind of a dilutional factor throughout the day. I don't know how that's looked like on the internet because there were a lot of people attending off site.

But I want to thank everyone for taking the time out of your very busy schedules. Many of you flew in from out of town, demonstrating to us the importance of this topic, and we really value your input. So thank you very much for your attendance.

I want to thank the speakers and the FDA leads for each of the sessions. You all provided a very informative overview of the regulatory science landscape for generic drugs, and I thank you also for taking time out of your schedules and for making such significant contributions to this workshop.

I want to thank the FDA session leads

because this was a bit of stepping out of a comfort zone for some people, so I want to thank them for coordinating the speakers and the panel members in order to construct such engaging sessions. So I think next year, we might have to figure out how to get coffee here early in the morning to get everybody jazzed up rapidly.

I also want to thank the panel members. I really appreciated hearing what you had to say, and I think your perspectives on some of these provocative areas were really valuable, as Rob and his group go back, and distill through all these comments, and decide how are we going to best spend a limited budget because there's no shortage of suggestions you guys give us. We usually end up with probably a billion dollars' worth of science, and we have in the low millions. So I thank you guys, the panelists, for all of your input.

I also want to take a minute to thank the people who work for Rob, the people in the Office of Regulatory Science. So if anyone's in the room who's in that group, can you just raise your hands?

(Show of hands.)

DR. UHL: A huge shout-out, thank you, to all of you guys. It was imperative to have them.

(Applause.)

DR. UHL: I was scripted to say thank you for volunteering to assist, but I would guarantee you that you were volun-told to assist on this workshop, and I thank you for that.

For those of you who are not part of the agency, you probably don't realize that putting together a workshop and putting together a part 15 are entirely different. A part 15 hearing is not that difficult to put together, certainly much more challenging to put together a workshop with panelists and such. And so it's a really huge lift to do that.

I especially want to thank Lieutenant Commander Murewa Oguntimein.

Is Murewa here? I don't see her hair, so I'm sure she must have stepped out.

Murewa made the Commission Corps proud. There is no doubt that this workshop would not have

been as productive as it was without Murewa. She did an exceptional job in ensuring that we had all the necessary volunteers. She worked extensively with the room coordination staff here at FDA about securing this room and about coordinating logistics, and a whole lot of work behind the scenes. So great job, Murewa.

I also want to thank the OGD communications staff for their support in promoting this workshop both internally and externally. So thank you to Jordana O'Grady and her staff.

The regulatory science program is a platform that allows for collaboration between FDA and our external stakeholders to provide tools to efficiently develop and evaluate generic drugs across all different types of drug product categories.

FDA and OGD will carefully consider all comments received today as well as submissions to the docket as we develop the fiscal year 2018 regulatory science initiatives under GDUFA, and that will then be for GDUFA II. Once approved by

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

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

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

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well as making internal regulatory decisions.

So we really thank everyone again for their participation. And I guess I'm the one who gets to say that today's meeting is concluded. So thank you very much and have a nice evening.

(Applause.)

(Whereupon, at 4:28 p.m., the meeting was adjourned.)

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