FOOD AND DRUG ADMINISTRATION

Generic Drug User Fee Amendments of 2012

Regulatory Science Initiatives:

Request for Public Input for

FY 2019 Generic Drug Research

Public Workshop

Thursday, May 24, 2018

8:30 a.m. to 4:03 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)

C O N T E N T S (continued)

P R O C E E D I N G S

(8:32 a.m.)

Opening Remarks – Robert Lionberger

DR. LIONBERGER: Good morning, everyone. I'm Robert Lionberger, the director of the Office of Research and Standards in the Office of Generic Drugs. I'd like to welcome all of you in the room and online to our FY 2018 Regulatory Science Initiatives Public Workshop. We welcome your participation in our process of identifying research priorities for the generic drug program.

Before we start the formal presentations, I'd like to go over some of the logistics for the meeting to remind you that this meeting is being webcast, recorded, transcribed, so take that into account when you make your comments. The recordings and the transcripts will be available on our website at some point after the meeting.

We encourage also the panelists to speak into the microphone so that the people online can hear you and our transcriber can also hear you clearly. We encourage people in the audience in

the room to silence your cell phones that you don't interrupt the proceedings. It's our intention to run the meeting on time and keep us on schedule and meet all of our breaks.

We'll be having a morning break. The important feature of the morning break is the morning break is the last time you can put your lunch order in at the kiosk, and then you can pick up your lunch order during the lunch break. We have space outside, if it's a nice day, to eat, but also we have rooms available behind the Great Room for lunch as well. But you have to put your lunch order in at the break, and you can pick it up during the lunch break. The restrooms are outside behind the kiosks as well. So again, we welcome all of you here today and thank you for your participation in this workshop.

As a reminder, our goals for this workshop are to get public input into the research priorities related to generic drugs. There are various ways that you can do this. Certainly, you're here, and at the meeting, as I said, we'll

be recording and transcribing the meeting, so anything that's mentioned here will be captured into the meeting. But as you're here and you're thinking and hearing things, and you don't have an opportunity to say something at meeting or you reflect on it afterwards, there is a public docket that's open for written submissions. This will be open for about a month after the meeting. We also welcome written comments from people who are attending online as well as people who are here in person. As you go back and reflect on what you've heard in those things that you think are important for us to consider in developing these priorities, please submit them to the public docket.

Also, if you refer to the Federal Register notice for the meeting, there is a description of a way that you can supply a confidential comment to the docket. So if that's something that's of concern to you or your organization, please note that process, and those comments are considered as well as we develop our regulatory science priorities. The priorities that are the outcome

from this meeting will generally be posted in approximately October of this year.

Today's format is going to be divided into two sections. Each section will have a panel with FDA industry and academic members on the panel in each session. We've invited some presentations and we have an open public comment period. After all the presentations, we'll have open panel discussions.

The topic and focus of the morning panel is seeking input on our current regulatory science initiative. Last year, we developed a large set of initiatives. We'll be giving updates on what we've been doing, but we're looking in the morning for feedback on those priorities; are they still on topic? Are there things within those priorities that we should be doing, and what's the most important thing that we could do immediately within those current priorities? I think they're pretty comprehensive, so it's a wide span of activities.

The afternoon panel is where we're looking for things that are not captured in our current

priorities; are there other things that we should be engaging in research on that are related to generic drugs? It'll help accelerate access to generic competition.

So that's the division between the two panels. In our very similar format, we'll start out with presentations. We'll have an open public comment period, and then we'll have panel discussions.

The panelists, as I said, we intend to run on time, but if there is time at the end of each speaker presentation, the panelists may ask clarifying questions at that time. I'll let you know if there's time for that based on any of the speakers, either the invited speakers or the public comments speakers. And then during the panel discussion, panelists may ask questions of speakers who presented earlier. I'll be the chair, and I'll call them back to answer the questions if that's something that the panelists would like further clarification on during the discussion process.

I just want to remind everyone the

significant impact of the research activities that come out of this type of meeting. Our research on complex generics helps the development of more generic competition, especially in the areas where the scientific issues are limiting competition, making development less efficient. This can be very significant across a wide range of product classes, and we're really interested in this meeting and identifying the areas where our scientific efforts can improve access to generic competition.

The second impact is more broader than that, thinking about just making the generic drug development process and review processes more efficient. This is why the GDUFA user fee program supports research activities, supporting access and the efficiency of development and review processes. So we welcome your input on how to do this more effectively throughout this meeting.

Finally, as you'll hear from our FDA introductory talks, there's a wide variety of activities that are ongoing related to these

research projects, and we'll only be able to give you maybe 30 seconds on each of our priorities today. But if you're interested in a deeper portrayal of the research results and how they link into generic drug development, I want to encourage you to save the date for a workshop that we're having just down the street in September, on the 12th and 13th.

This is a two-day workshop of FDA presentations. It'll go much deeper into the technical details of the research activity that's been supported by the user fee program and link those research outcomes into product development and how to interact with FDA through the new GDUFA pre-ANDA meetings for complex products. So I encourage you to save the date for this workshop for much more technical and deep presentation of our research activities.

For our first talk today, I'd like to introduce my office deputy, Dr. Lei Zhang. She'll be talking about our work on the FY 2018 research.

Welcome, Lei.

Presentation - Lei Zhang

DR. ZHANG: Thanks, Rob.

Good morning. As Rob mentioned, I'm going to give a very high-level overview about our FY 2018 research update on our research initiatives. This slide summarizes the four broad categories of our FY 2018 GDUFA priority areas, which was generated from our discussion in May of last year. As you are aware, we have this workshop every year to discuss, and through the discussion, there were also comments received.

We summarized into 15 priority areas under four broad categories. As you can see, the first three categories are focusing on the complex generics category. Complex generics, as you are aware, is defined in the second cycle of Generic Drug User Fee amendment, GDUFA II, as complex active ingredients, formulation or dosage forms, complex routes of delivery, complex drug-device combination, as well as some other complexity or uncertainty associated with those products that early engagement with FDA will benefit. Under

GDUFA II, we do have the pre-ANDA meetings mechanism to facilitate this engagement and discussions early on.

The fourth category, we're focusing on the tools and methodologies for bioequivalence and substitutability evaluation as always, because as you can see, although we have some new initiatives generated in FY 2018, a lot of areas are a continuation of the prior first five years of GDUFA I research activities.

To guide you through the outline of today's presentation -- because I only have 20 minutes, so I want to give you a quick overview of each product area -- I grouped the content into the following order: FDA internal research and our external collaboration through contracts or grants for both FY 2018 as well as for potential FY 2018 grants and contracts. For 2018 or 2017, we also have some grants, contracts, or ongoing research that received funding in 2017, as well as some new contracts initiated in 2017.

I also want to give you some quick overview

of the outcomes generated from those research activities through public workshops, publications, guidance development in terms of both general guidances as well as product-specific guidances. All of these, the research and science, are the foundation for our review decision-making, helps the guidance, as well as a review process. And ultimately, we hope that can lead to ANDA approvals and also make the medicine available to the American public.

The first broad category focuses on complex active ingredients, formulations, or dosage forms. Under this category, we have five priority areas. The first priority area is improve advanced analytics for characterization of chemical compositions, molecular structures, and distributions in complex active ingredients.

In terms of FDA internal research, we have research on characterization of complex active pharmaceutical ingredients, APIs, including polymeric drugs, oligonucleotides, and peptides. In addition, we also have research to characterize

polymeric excipients; what are the critical quality attributes that can help us in generic drug development.

We also have ongoing grants and contracts in 2017 focused on studying one of the complex products, which is penstosan polysulfate sodium and how we do bioanalysis assays to help the bioequivalency establishment.

We also held public workshops last October to talk about the demonstration of the equivalence of generic complex drug substances and the formulations, which support this research priority area. If you want to know more detail, you can go to the website to learn more information. We also have published one general guidance that focuses on the ANDAs for certain highly purified synthetic peptides that refer to the Listed Drugs, which are of rDNA origin. We also have PSG development for one of the sucralfate oral suspension products. Just last year, we had three first generics, ANDA approved, that covers the complex API product.

The second priority area focuses on improved

particle size, shape, and surface characterization to support demonstration of therapeutic equivalence of suspended and colloidal drug products. As you can see, we have a lot of FDA internal research, which I'm not going to read through, but they include quantifying albumin instructor changes due to the manufacturing process and the corresponding changes in binding affinity to paclitaxel and also quite a few focusing on liposomal formulations.

In addition, we have research to study the particle size characterization for APIs in suspended based aqueous nasal spray products using morphological directed Raman spectroscopy MDRS, as well as new methods of equivalence testing of complex particle size distribution profiles using the Earth Mover's Distance method. These have been described in two public workshops. One I mentioned earlier in October 2017, and another one, we just had early this year in January on new insights for product development and bioequivalence assessments of generic orally inhaled and nasal drug products. We also have multiple publications. In addition,

the PSG, product specific guidance development, for certain complex products. Last year, we also approved the second doxorubicin liposomal product. As we are aware, this drug was in shortage.

The third priority area covers established predictive in silico, in vitro, and animal studies to evaluate immunogenicity risk of formulation or impurity differences in generic products. We have some FDA internal researches focusing on immunogenicity assessment as well as impurity profiling for the oligonucleotide products as well as peptide products.

We also considered some potential grants and contracts in this fiscal year to evaluate the immunogenicity risk. This has been discussed at a public workshop, and also I mentioned earlier there's peptide guidance that was published last year.

The fourth area covers develop predictive in vitro bioequivalency methods for long-acting injectables. FDA has internal research studying the in vitro BE method for suspension injectables,

and we have in 2017 ongoing grants and contracts, four grants and two contracts, on long-acting injectable modeling, PLGA peptide interactions, and PLGA characterizations.

In addition, we funded two new contracts in FY 2017 that cover in vitro/in vivo correlations of allowing long-acting injectable suspensions to improve scientific approaches to evaluate generic drugs, as well as development of analysis technique for structural characterization of star-shaped polyesters used for drug delivery.

We also considered two additional potential grants and contracts in FY 2018. You may not be able to read all the content at this point, however, the slides will be available after the workshop and posted online. We have the public workshop as well as publications that cover this area. There's a PSG on leuprolide acetate intramuscular injectable depot published just February of this year.

The fifth area under this category is develop better methods for evaluating abuse

deterrence of generic solid oral opioid products, including in vitro alternatives to in vivo nasal and oral studies. The FDA has many internal research covering this area. They are lab-based projects covering technical profiles of reference listed drugs; determination of syringeability and injectability; in vitro manipulation and extraction studies; nasal powder characterization; nasal regional deposition model; and chewing IVIVC model.

In addition, we have quantitative analysis ongoing that aim at IVIVC development of opioid products using in vitro chewing methods and PDPK modeling and advanced PK modeling of opiate following nasal insufflation of physically manipulated products using the 3D CFD model, regional deposition dissolution and diffusion studies. In addition, the PKPD relationship of abuse-deterrent opioid products is being studied. These all helped develop our general as well as product-specific guidances.

We also had a contract in 2017 studying the nasal PK study of opiate following insufflation of

physically manipulated product, which is OxyContin. This study was just completed and PK results were obtained. You may learn more results in our later workshops.

We also considered at least two potential grants and contracts in 2018 studying nasal PKPD studies with oral agonists and antagonists combination products as well as oral chewing PKPD studies with those oral opioid products. We have a publication in this area as well as we just finalized our general guidance on general principles for evaluating the abuse deterrence of generic solid oral opioid drug products last year, and based on the principle in this general guidance, we are also developing product-specific guidance for those ADF oral opioid products.

Now I'll move on to the second category, which is complex routes of delivery. Under this category, we also have five priority areas identified. The first is improved physiological-based pharmacokinetic PBPK models of drug absorption via complex routes of delivery.

Those include nasal inhalation, dermal, and ophthalmic products. All these are locally-acting drugs, which using traditionally PK BE methods may be challenging. So we have FDA internal research focusing on topical area as well as ophthalmic area, inhalation, nasal, and locally-acting products in general. So we have many research ongoing in this area.

Also, we have ongoing grants and contracts funded in FY 2017, three grants for CFD-based modeling of lung deposition; one grant for CFD and PBPK model for nasal products; two grants to advance ophthalmic PDPK modeling; and two grants to advance topical transdermal PDPK modeling. So we covered all the local complex routes of delivery. And we also have more projects and grants planned for potential FY 2018 research. These include the formulation drug product quality attributes in dermal PDPK models for topical products and also the skin physiological parameters that can be utilized in dermal PBPK model in the different disease states and also CFD and discrete element

modeling approach for prediction of dry powder inhaler drug delivery and 3D approach for modeling nasal mucociliary clearance via CFD, and also potential contracts to support our continued development of the CFD and PBPK models, and in addition, some in vitro and animal studies to help support our model.

We have many publications in these areas as well. What I want to highlight here is that we are going to have an upcoming public workshop focusing on PBPK modeling for locally-acting products that will be held in March of next year in conjunction with the ASCPT, the American Society for Clinical Pharmacology and Therapeutic annual meeting.

The seventh area is to expand the characterization-based bioequivalence methods across all topical dermatological products. We have FDA internal research in the development of novel biorelevant in vitro skin permeation tests using in-line flow through diffusion cells and also manufacturer of AT-rated topical ointment formulations for in vitro release-test method

validation. And we have quite a few ongoing grants and contracts funded in 2017 to expand our characterization-based BE methodologies across petrolatum-based topical ointments, including those AT rated ointments and also grants to advance our in vitro cutaneous PK BE method and expand those characterization-based methods across all topical dermatological products. And we have grants to develop in vivo cutaneous BE studies using dermal microdialysis and microperfusion clinical studies to expand our ability of those novel efficient BE methods across all topical dermatologic products, including those non-Q1 and Q2 products.

We also consider a few under FY 2018 grants and contracts focusing on bioequivalence of topical products and also establish a correlation between local and systemic drug concentration, leveraging the dOFM data. We had a public workshop to summarize our past five years research in this area, in the topical dermatologic generic drug products development, how we are overcoming the barriers to development and improving patient

access in October last year. We also have publication in this area, and we will have more in the publication to summarize our research in the next few months.

In terms of the outcomes, we do see in this area these are quite a few product-specific guidance being developed. We expanded beyond this in vitro novel BE approach from one product to multiple products. So this slide highlights those product-specific guidances being developed just last year. Also, we have quite a few ANDA approved last year in these topical dermatological areas. I would like to highlight especially the acyclovir topical ointment product.

This product, the RLD was approved in 1986, so for over 30 years, no generic was approved until 2012 when we published our PSG for acyclovir. Since then, in the six years, we have approved 8 total generics for this product with 4 of them approved the last year. So we can see how the novel BE approach method can facilitate generic drug development so that the sponsor or applicant

does not need to rely on those in vivo comparative clinical endpoint studies, which could be quite challenging. Also, last year we had four more first generics approved in this therapeutic area.

The eighth product area covers expanded characterization-based BE methods across all ophthalmic products. FDA internal research covers asymmetric flow field flow fractionation measurement of cyclosporine ophthalmic emulsion, and also used unit dose content testing and particle size distribution tests for ciprofloxacin and dexamethasone ophthalmic products.

We evaluate physicochemical testing of non-Q2 ophthalmic solution products and also evaluate rheological properties of in-situ forming ophthalmic gels and what's the impact of those excipient grade and dilute media composition, and we use the animal model to study the ocular biodistribution of those products and what's the impact on the formulation viscosity and particle size. We assessed the in vitro release testing method for those ophthalmic emulsion products. We

have ongoing grants and contracts in 2017 to study the pulsatile microdialysis for in vitro release of those ophthalmic emulsion products.

We consider potential FY 2018 grants and contracts on the in vitro studies, which are tissue-based assays for ophthalmic topical products. We covered our research in the October workshop last year and also have publications. In addition, we have developed product-specific guidance that incorporates those in vitro approach supported by our GDUFA research. And on this slide, I show two of the examples, which is the fluoromethalone ophthalmic suspension, as well as the loteprednol etabonate ophthalmic suspension product.

Now, I'll move on to the ninth area, which is develop more efficient alternatives to the use of forced expiratory volume in one second, which is FEV1 comparative clinical endpoint BE studies for inhaled corticosteroid product. We all know this is a very challenging area to develop generic drugs, so FDA internally has research biorelevant

methods for assessing quality and the performance of inhalation products using the realistic mouth-throat model for studying the deposition. We have ongoing grants and contracts for PK study on dry powder inhaler. This study was recently completed, and also we have a grant for PK study on metered dose inhaler.

The new FY 2017 contracts include one contract on investigating the microstructure of dry powder inhalers using orthogonal analytical approaches. We also considered quite a few FY 2018 grants and contracts mainly using the CFD model approach for prediction of dry powder inhaler drug delivery and also the development of empirical models and in vitro methods for the prediction of batch-to-batch variability of dry powder inhaler formulations and also study the characteristics of tracheobronchial models of adult female and male chronic obstructive pulmonary patients for CFD analysis.

The research in the past five years has been summarized in the public workshop in January of

this year. We also have quite a few publications in this area. In terms of the guidance development, we have developed six new product-specific guidances covering different dry powder inhaler and also inhalation aerosol products. And as we are aware, there are no generics being approved in this area, so we hope with research we might have more products being approved in the near future. But we do use the research to engage a lot of pre-ANDA meeting discussion with the sponsorS at this point.

The tenth area covers developing alternatives to comparative clinical endpoint BE studies for locally-acting nasal products. FDA internal research includes particle size characterization methods for API in suspension-based aqueous nasal spray products using the MDRS and also meta-analysis of in vitro BE data submitted in the ANDA application for those nasal products. We have a contract for nasal PK study, and also we granted a new contract in FY 2017 to investigate orthogonal analytical approach to

demonstrate the BE of nasal suspension formulations.

We consider in 2018 to have grant contracts to improving in vitro tests for clinical relevance, those nasal models, and also the 3D approach for modeling of mucociliary clearance via CFD. We had a workshop in January 2018, and also we have two new PSGs in this area, plus one ANDA was approved in the last year.

Now, I'm going to move on to the third category, which is complex drug-device combination. This area, we only have one priority area to evaluate the impact and identify differences in the user interface on the substitutability of generic drug-device combination products. This area, we don't have too many researches. We just had some new that were initiated in a patient perception of dry powder inhaler airflow resistance, and also we consider a potential contract on patients' perception to device substitutions. One highlighted is that we are going to have an upcoming public workshop to cover the complex

generic drug-device combination products in collaboration with DIA. This workshop will be in October of this year.

The forth category focuses on tools and methodologies for BE the substitutability evaluation. Under this category, we have four priority areas. The first one, the number 12, is improve quantitative pharmacology and bioequivalency trial simulation to optimize design of BE studies for complex generic products. So as I listed on this slide, there are quite a few PKPD, which I also mentioned earlier for ADF opiod products and also for locally-acting drug products, so I'm not going to repeat here. Many of them do support various complex products that I mentioned earlier.

Also, we are going to have a new -- we did fund a new contract in evaluation and development of model-based BE analysis strategies and also the new contracts, we will consider BE evaluation of nanoparticles and molecular medicines, and also using PDPK and PD models for intrauterine device to

evaluate those alternative BE approaches, and also alternative BE for long-acting products.

We had a public workshop talking about those quantitative methods in modeling in October of last year, and also we have quite a few manuscripts, and here are two examples. Also, the modeling methods has helped 46 PSGs in last year, and here's the example on ivermectin topical cream and the naloxone nasal spray. Also, the modeling has helped with the brimonidine topical gel tentative approval last year.

The 13th category area include integrate predictive dissolution PBPK and PKPD models for decision-making about generic drug bioequivalence standards. This is continuation research. As you can see, we have many internal research focusing and assessing the impact of dissolution profiles on PK and BE, and also chewing device on abuse-deterrent assessment; identify drug interaction mechanism of modified release product and proton pump inhibitors, and also identify rate-limiting step for Omega-3 ethyl ester

intestinal absorption and multivariate similarity testing for multi-batch dissolution profiles.

So there are also many grants and contracts on studying the supersaturation models, in vivo predictive dissolution methods, wireless analysis device to measure in vivo drug dissolution, and also PK studies for IVIVC for amorphous dispersion, and PK study on proton pump inhibiting interaction, and also the contract for MRI measurements of GI water content and grants for PKPD studies on metoprolol and methylphenidate. This research area mainly focuses on the oral dosage form and especially those extended- or modified-release products.

We have a new contract to study the phase behavior and the transformation kinetics of a poorly water soluble weakly basic drug upon changing from low to high pH conditions and also potential grants to develop a virtual BE trial simulation platform that can integrate those population PK modeling algorithms into PBPK models and also evaluate relative bioavailability in

special populations such as pediatric patients or products, and establish alternative BE methods by integrating those sequential designs and Bayesian methodologies. In addition to the public Workshop and a manuscript, the research has supported prasugrel -- one example is prasugrel hydrochloride tablet approval last year.

The 14th area includes expanding the scientific understanding of the role of excipients in generic drug products to support expansion of the BCS class 3 biowaiver to those non-Q2, which is quantitatively inequivalent formulations. Though this is a challenged area, we want to see if the research can help support the regulatory path forward. So FDA internal research includes bi-phasic dissolution systems, studies and impact of excipients on drug solubility, passive permeability, and intestinal metabolism and transporter. We also have a database on commonly observed excipients in immediate-release products for BCS class 3 drug products, and we have ongoing contracts for effective excipients on intestinal

drug transporters.

Here's a list of publications in this area as well as our presentations in the national meetings. As you are aware, FDA has finalized the guidance on waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage form based on the BCS classification system last year, and there is ongoing ICH harmonization going on with other regulatory agencies.

The last area focuses on developing methods that will allow FDA to leverage large data sets such as BE study submissions, electronic health records, substitution and utilization patterns, and drug safety and quality data for decisions related to generic drug approval and also postmarket surveillance of generic drug substitution. So we have internal research on machine learning and neural network analysis to predict the association between kinase targets and adverse reactions, and big data analytics for postmarketing signal detection. And there's ongoing research funded in

FY 2018 on the use of pharmacometrics for postmarket surveillance. And we will consider some potential grants in 2018 on generic utilization and the substitution of thyroid agents as well as machine learning for IVIVC PK and PD analysis. So there's a public workshop to discuss our research tools as well as publications.

Finally, I just want to give you a quick overview on the research outcome just from the last workshop to today. We have held five public workshops, and there are 29 research related publications in FY 2017, and up to now, we have 19 already in the research area. There are three general guidances published last year, as well as 229 product-specific guidances developed. Sixty of them are for complex generics, which is about 26 percent. Also, between April last year and March this year, we have 80 first generic approval. Among them, 18 of them are complex, which is about 23 percent. We see that 15 out of those 18 first generics have PSGs. So we want to continue to develop PSG to support the ANDA drug development

and approval.

This slide summarizes the three future workshops that will be co-sponsored by the FDA. The first one, Rob mentioned it, and I also mentioned about a DIA workshop on complex drug-device combination products as well as the PBPK modeling for locally-acting products.

This is just a quick snapshot on the GDUFA science and research website. You should use this as your resource to learn more about our research. This is a new look, so we have four categories focusing on priorities, projects, research publications, and resources, guidance and reports, and collaboration opportunities. So this will have a lot of information if you have more interest.

Finally, you can see we have a lot of research going on. It's great teamwork. I would like to thank the Office of Research and Standards staff who conducted the research, as well as our external collaborators both within and outside of FDA, as well as OGD policy and OGD comm staff to make this presentation. Thank you.

(Applause.)

DR. LIONBERGER: Thank you, Lei.

So as you see, we have a wide variety of activities related to our research priorities, and so we're committed to report on the priorities that we identify and act on all of them. Our next talk will be by Stephanie Choi, who is the acting associate director for science. And she'll talk about research metrics for GDUFA II reporting.

One of the new aspects of our GDUFA II commitment letter is reporting on research outcomes, and Stephanie will begin to outline how we're planning to do that aspect of this. As you can see, there's lots of activities, so we want to make sure it's easier for people to find what those activities are and how they're related to outcomes relevant to the generic industry.

Welcome Stephanie.

Presentation - Stephanie Choi

DR. CHOI: The GDUFA II commitment letter describes reporting of research projects that support the review and development of generic drug

products. In my presentation, I will describe some proposed research outcome measures that could be used to evaluate the impact and progress of GDUFA-funded studies. All the data that I will be presenting in my presentation actually comes from GDUFA I awarded studies because we have not yet made the bulk of the awards for this fiscal year yet, which is the first year of GDUFAII. But in doing so, hopefully it will give us an idea of whether these measures are appropriate to assess projects that we award during GDUFA II.

Since the first year of GDUFA, we have awarded 36 research contracts and 69 grants. The table below gives a breakdown of the number of projects awarded by year. We also have a significant number of ongoing projects because many of the projects are on multiyear timelines and receive funding for more than one year. I also want to note that there are many projects not captured in this table because they are on no-cost extension, so work is ongoing but no award is associated with those projects. We have a

comprehensive list of all the grants and contracts that we've awarded on our GDUFA Regulatory Science webpage.

The GDUFA II commitment letter really has a heavy emphasis on complex drug products, but actually since the start of GDUFA I, we have been consistently awarding more than half of our external research projects on complex drug products as seen in this table. In addition to collaborating with external collaborators such as academiae and industry, we also have a number of internal research studies with various FDA offices and laboratories, and we have completed 80 research projects and also have 40 ongoing projects with various centers and offices throughout FDA.

This slide shows the number of external projects awareded for different types of complex drug products and it shows that we've made significant number of awards for many locally-acting drug products such as inhalation, ophthalmic, topical, and transdermal. We've also made many awards for complex products administered

by the injectable route.

This data is for internal projects that have been conducted for different types of complex drug products. It shows a fairly similar distribution, and this is just a combination of both the internal/external projects to give an overall picture of the total distribution.

The GDUFA II commitment letter includes a section on regulatory science enhancements, which describes a type of reporting by FDA on GDUFA-funded projects. It describes three types of reporting, reporting on how projects support the development of generic drug products; reporting on how projects support the generation of evidence needed to support efficient review and timely approval of ANDAs; and how project support the evaluation of generic drug equivalence.

So to evaluate how projects support the development of generic drug products, we could look at pre-ANDA meetings as a potential outcome measure. Some potential metrics for this could be the number of pre-ANDA meetings received, the

number granted, or the number completed for a particular drug product that has been studied in a research project. Similarly, we could look at control correspondences, the number received, the number completed, as well as product-specific guidances, the number of guidances newly developed or revised for a particular drug product that is tied to a research project.

To look at the generation of evidence needed to support review and approval of ANDAs, we could look at ANDA submissions, as well as ANDA approvals for a drug product that is tied to research, and for the evaluation of generic drug equivalence, we could look at postmarket studies conducted on our drug product or a class of products and look at the impact and results from these studies, as well as the extent of scientific communication. This would include things such as publications at scientific journals, presentations given at scientific conferences, as well as webinars and public workshops.

Some of the research outcomes that we

started to track for our research projects include the extent of scientific communication, guidances, which include the product-specific ones as well as the general recommendations to industry; regulatory submissions, including ANDAs; pre-ANDA meetings; control correspondences; and citizen petitions. And we also look at databases, tools, models, which are generated from our projects that we share publicly. Some examples are the UCSF Excipients Browser on molecular excipients, which allows one to search for an excipient to look at predicted effects on bioavailability and bioequivalence. We have also shared codes on statistical analysis through our PSGs.

On our GDUFA Regulatory Science webpage, we have posted lists of different journal articles, presentations, and posters that have been presented not just by FDA staff but by our external collaborators. And the numbers in this table are drawn from the list that we've posted on the website. Every year, we publish in a wide variety of different scientific journals, and we also have

our staff attend and give presentations at different scientific conferences. In recent years, we've also held a number of public workshops focusing on different topic areas, and these workshops provide a forum for FDA to discuss the latest research updates as well as future needs for research to address scientific gaps.

Research has informed guidance development and pre-ANDA communications with industry. Scientific research can inform PSG development by providing understanding of the development and evaluation of novel analytical techniques, methods, and assays. Analytical techniques are constantly changing and improving, so we need to conduct research to keep up with the latest and newest technology so that we can evaluate them for utility and evaluation of bioequivalence.

Research also allows us to perform in-depth characterization of the reference listed drug. This way we get better understanding about the physicochemical properties of the drug product, and many times it has allowed improved in vitro test

recommendations in our PSGs. These types of research many times lead to increased use of alternative approaches to demonstrate bioequivalence, where in vitro approaches may be recommended as an alternative to in vivo studies or as a supplement to the in vivo studies.

We have developed more PSGs across a spectrum of different therapeutic categories, especially for complex drug products that lack generic counterparts, and I will be showing some examples of this in the next slide. Research has also informed communications with industry during the pre-ANDA stage by providing scientific knowledge, which will help us in the review of pre-ANDA meetings and control correspondences.

As an example of how research has contributed towards PSG development, this slide shows a number of new and revised PSGs for different types of complex injectable drug products. Before the research program started in 2013, we had PSGs posted for some of these categories but not in very high numbers. And after

start of the research program, the number of new and revised PSGs for many of these categories increased significantly. And actually, many of the PSGs that we posted prior to 2013 were revised after 2013 based on scientific knowledge gained from our research studies. The numbers in green indicate the number of research projects that have been awarded for that particular category, and they show a link between the level of research effort and the number of PSGs that are developed.

Another example is in the category of ophthalmic drugs. Non-solution ophthalmic products such as ointments, emulsions, and suspensions lack generics, and one reason is that the in vivo study can be very difficult to conduct and also pass bioequivalence limits. Before the research program, we did not have any PSGs that outlined an alternative in vitro approach to demonstrate bioequivalence. With the start of the research program, we awarded 10 external projects and have conducted 19 internal projects to assess various in vitro tests for the assessment of bioequivalence.

As a result, we've been able to post PSGs for different non-solution products, and this also provides greater opportunity for generic drug approval.

This slide shows the linkage of research projects, both internal and external, to the number of pre-ANDA meeting requests received for different types of complex drug products. Some categories such as injection, nasal, ophthalmic, topical, and transdermal, they show similar numbers of research projects to the number of meeting requests received. Other categories such as the inhalation, products with complex APIs show lower numbers, but we would also consider other outcomes such as the impact on PSGs, ANDAs, scientific communication to properly evaluate the additional research needs for these categories.

I would also like to describe some notable first-generic ANDA approvals that came about through research. One is glatiramer acetate injection. The approvals came about through several internal studies that were performed on

characterization of the API, and this data allowed us to understand which tests and comparisons are appropriate for evaluation of a test and reference product.

We also conducted several internal and external studies on the local PK and bioavailability of mesalamine, which eventually led to a PSG that recommended additional partial AUC metrics for the PK study and the first generic approval for the delayed release tablet last year.

For mometasone furoate nasal suspension, we conducted a series of internal studies on morphologically directed Raman Spectroscopy, which is a novel particle sizing method, and by performing these studies, we were able to evaluate this new technology and accept in vitro studies in lieu of the in vivo clinical bioequivalence study for a complex nasal suspension product.

Lastly, I would like to end my presentation by providing the link to the GDUFA Regulatory Science webpage, which includes all of the items listed here, as well as research outcomes that we

will be posting for our GDUFA II studies. So we encourage you to check this page regularly for updates. Thank you.

(Applause.)

DR. LIONBERGER: Thank you, Stephanie.

So again, this is a new commitment in GDUFA II, so we also welcome comments to the dockets on things that you think would be helpful in terms of developing the future reporting as well. So it would be appropriate to make those comments to the docket as well here.

Now we'll be changing gears and shifting to presentations from -- we've heard our FDA perspective on some of the research that's ongoing. Now we turn to hearing from both industry and academic perspectives on what we should be doing in these priority areas. Our first speaker from the generic industry is Theofanis Mantourlias from Fresenius Kabi, talking about complex drug products. Welcome.

Presentation - Theofanis Mantourlias

DR. MANTOURLIAS: Good morning also from my

site. Thanks a lot for this invitation and being here. I'm Theofanis Mantourlias, leading the formulation development group of the European IND of Fresenius Kabi located in Austria. I would also like to thank the authorities for inviting us here and the Association of Accessible Medicines and the more specifically Lisa Parks that made this come true.

In general, I will speak, again about complex drug products, what we consider and what we mean about complex in this case and in our today discussions, and more specific about how we can gain the bioequivalence without clinical studies. A little bit about the current studies, how can we reduce the BE studies or eliminate? How can we do this, maybe the way out, a way forward, and a glance to the future, and some conclusion remarks.

So for our today discussions, we will talk about complex products. We will talk about complex drug substances or formulations that present a lot of challenges in demonstrating the sameness and equivalence with the reference listed drug.

The complexity can either come from the API, as we heard in the morning, highly synthetic peptides, polymeric compounds, or it can also come from the formulations, suspensions, emulsions, in situ forming gels, and polymeric microparticles. We've heard a lot of examples in the morning, in the previous slides.

So the current studies is according to the current guideline. The bioequivalence or the biowaiver is an open window. In most of the cases when we talk about solutions, injectable or parenteral solutions, of course all the sustained, delayed-release and extended-release drugs are right now excluded from this guideline, from these regulations.

As we heard previously, also companies, we salute this good approach from the authorities. I also took the example for the PLGA based products, that right now, there are a lot of research projects initiated by the authorities in collaboration with universities, so we can gain more knowledge about these products, about the

in vitro/in vivo correlations, new in vitro dissolution methods, characterization of these products and modeling of course, and simulation. This is from our side, also perfect, initiative, and it's always a way forward. So we can see also publications coming out and probably more product-specific guidance coming out from these collaborations.

Why do we need to reduce the BE studies, the bioequivalence clinical trials? Because from the same regulation, we see that no unnecessary human research should be done, and it's not ethical, specifically when it comes to products where non-healthy subjects and non-healthy volunteers can be used, we have to go with patients, and then it becomes even worse.

Also, from a point of view, it does not mean that clinical trials also introduce or are on the way of making better products because there was in the past the thinking, sometimes the black box thinking, on a bioequivalent injection, we don't understand fully the mechanism, what is behind,

what is the release? As soon as we are bioequivalent, sometimes we miss a lot of information and a lot of physicochemical characterization.

In terms also of generics, the time and the cost of drug development is a huge one. Clinical trials are in place. For example, there are a lot of cases that although the companies could go into development of such products only by knowing the risk and sometimes the high cost, especially when patients are used for clinical trials, they drove back and they are not involved in the development of generics because, to be honest, it's a high risk.

Again, as I mentioned, the bioequivalence studies come to the point later that you have changes in maybe the manufacturing process or some changes of site. Again, with bioequivalence studies in the case if you haven't very good in vitro/in vivo correlation, then you have to perform it again. Again, new people injected for the same product.

Of course, also something that I want to address is that for these complex products, we can see also products -- we can see a lot of batch-to-batch variability for the reference product as well. I have included here an example for suspension, two generic products authorized to be on the market, the same bioequivalence study, the same strength, the same everything. You can see that, for example, also for the reference product, both of them, they are bioequivalent with the reference products, but you see that there are some differences, for example, in the Cmax.

So we see that for such complex projects, you see some deviations, some differences also for the reference products because they are based, for example, on the API, on the particle size of the API, and of course API suppliers they don't have also strict limits.

How can we reduce BE studies? For example, right now we have the new guidelines. We have the development by design, the quality by design. This is definitely the way forward. The RLD and reverse

engineering, in-depth characterization of the reference listed drug, not only in terms of identifying the critical quality attributes, but right now we are in the position to understand fully the manufacturing process, the sterilization process, how it is performed. For example, we have a lot of measurements to understand what is part in encapsulated APIs, if the API is in crystalline form, or if it's a amophrous form, porosity, specific surface area, and very deep characterization right now for the manufacturing.

Sometimes I was understanding better the product from the RLD because we really try to to investigate, be the science, and investigate really in depth. Of course, the quality by design, this is the only way forward to develop products very good of quality and safe. In the occasion of critical quality attributes, link them to critical process parameters. And right now, we are in the good position that we have very good analytical tools. So right now there is a huge progress in science, and we have good analytical tools.

So right now for one measurement, for example, for particle size distribution, you don't have to stick to one method. You can use different methods or you can find the truth, because for each and every method, there are limitations. Some methods are good for bigger particles, but you lose part or a fraction of your small particles. But really, we have to combine the methods. We have to combine in order to understand it fully.

Of course, in order to be able to reduce the BE studies, the most important way forward is the in vitro dissolution method, and of course the correlation with in vivo. This is really very important. Right now, we are going away from the QC methods, in vitro QC methods. Previously, we could see only the in vitro methods, that they had the very big ranges. For example, at day 15, no more release than 80 percent or something like this, but right now the dissolution methods are becoming more discriminative in power in terms of critical manufacturing attributes or critical process parameters. So we try right now to have

methods that are really discriminative, although sometimes they are very slow or they take longer. But nevertheless, it's very important to basically develop such methods.

Of course, we can use animal models, animal studies, and have a good in vitro/in vivo correlation, and we can use animal studies, for example, also during scale up from the lab to pilot to commercial, and we can link them with a good IVIVC model and prove that the product is bioequivalenct.

Last but not least, the generic driven scale up approach, right now, again, there is the modeling. We can monitor part of the process, of the manufacturing process or even the whole manufacturing process. From my side or from my point of view, we can also increase in process controls to be more safe and to bridge also the commercial and the lab scales. This is definitely right now using scaling up factors, designing equations for the equipment, fully understanding. And right now, what we see is that also the

suppliers of the equipment are more cooperative. They really have their own R&Ds, and products that are really difficult to handle, or to dry them, or to filter them, they're really right now working with us side by side in order to improve the manufacturing equipment and have scalability.

So what will probably in the future? Also, what we had in the morning, in silico trials, they're very, very important. Right now, we have -- probably in the future, there are no more humans but virtual organisms. I have an example here. HumMod is one of the most advanced simulation tools, that they simulate the physiology, the human physiology.

So definitely it's a way forward because we can even reduce the size and the duration of these clinical trials. We can predict interactions long term that you cannot see with one clinical trial, and you can predict what will be the future. The final aim, of course, is to complete substitution of the clinical trials. For example, if we know the release mechanism of a complex drug, and if we

can simulate it and model it, then we will have another tool.

Also from the future, we know that right now the future is going to more specific, patient-specific drugs. We know that the medication does not work for each and everyone the same. We see also from the clinical trials the standard deviations. So from my side, just increasing the number of subjects just to gain bioequivalence is statistics, but we have to move forward.

My conclusions for this is that right now with existing regulations, the complex drug formulations like suspensions, extended release are right now excluded. From our point of view, also the biowaiver options should be included for such complex drugs to avoid clinical trials to reduce reliance on in vivo bioequivalence studies.

What we know is that right now, we have to pay more attention with in vitro characterization to have correlation with the physicochemical characteristics. We have a very good correlation

with the in vivo. And probably also, as we heard with the guidance of the authorities, that we have more specific product guidance. This will also help. And what we will face in the future probably will be more in silico clinical trials, a lot of modeling based simulation, and I hope this is the way forward. Thank you very much.

(Applause.)

DR. LIONBERGER: Thank you very much. We don't have time for questions.

Our next speaker from industry is Prasad Peri from Teva, talking about inhalation drug products.

Welcome, Prasad.

Presentation - Prasad Peri

DR. PERI: Thank you.

Good morning, everyone. Thanks To Dr. Choi and Dr. Zhang. They made my presentation very easy, and all I will do is outline what the FDA has done in terms of public meetings and their initiatives, and how we can move that forward from an industry perspective, as well as from a general

regulated perspective.

Recent activities, meetings for OINDPs, FDA sponsored and participated in several conferences, especially the one in January on new insights for product development and bioequivalence assessments. Some of the topics that were discussed were predictive dissolution methods for OINDPs, novel analytical tools for characterization of nasal suspensions, realistic models for predicting the regional drug deposition, and of course computational models to understand the in vivo models and future directions.

The outcomes of these presentations were the relevance of in vitro dissolution methods and deposition studies and their impact on the PKPD and the key challenges to the in vitro only BE pathway for nasal suspensions and orally inhaled products. I think Dr. Guenther Hochhaus is going to be presenting gaps of what is remaining and what needs to be done to be able to bridge and get an in vitro and BE perspective to be able to approve a product without doing clinical studies.

So the IFPAC conference symposium, again, the team of that was critical attributes of orally inhaled products link between in vitro properties and therapeutic performance, extending the MAM/PBPK modeling approaches to help establish inhaled product specifications, working towards real time assurance of clinical performance, formulating for PAT and leveraging IVIVC capabilities. So again, summaries and assessment of in vitro methods, PK modeling to develop in vivo IVIVCs and their predictions on pharmacodynamic parameters.

Recently again, there were two presentations made by Dr. Robert Lionberger and Kim Witzmann, and the titles are appropriate in terms of New Tools for Generic Orally Inhaled Products to Maximize the Prospects for Food and Drug Administrationi Approval, and The Role of Comparative Analysis for Evaluation of Generic Drug Device Combinations in an Abbreviated New Drug Application. Following that, there was a panel discussion in terms of expanding the generic marketplace via improved testing protocols and

regulatory guidance.

So what are, in general, the brief outcomes for these complex respiratory in vitro demonstrations of equivalence instead of clinical studies? The points to address, are there many possible product attributes that can be measured by a variety of techniques to show in vitro properties? For example, particle size, shape, properties, APSED, emitted dose, powder flow, etc. Some of these properties could be shown to have a link to in vivo performance. Others perhaps are just easily measured but do not really impact another pharmacodynamic performance. So we want to ensure that we are actually characterizing the relevant properties or parameters for a drug product and how it relates with the pharmacodynamic performance.

Again, the most desirable area from an AAM perspective is to address the elimination of clinical endpoint bioequivalence studies, and these are typically costly expensive, a hundred to over a thousand patients. So the clinically relevant in

vitro tests could be developed and validated to support this. And we are happy that FDA and other partners are actually looking towards this. Going forward, hopefully this is a very important area for AAM and other pharma companies in general, and I hope the research and development activities continue.

The recommendations from my perspective, in terms of AAM, is we hope that the agency continues to sponsor programs that enhances a deeper understanding of the impact of critical material attributes, critical process parameters and analytical procedures on clinically relevant parameters for inhalation products. FDA science should aim to narrow down the plurality of potential equivalence attribute comparisons and to those that have a clear link to in vivo performance. Comparisons to show IVBE should be readily measurable by widely available techniques where the validity has been established. And FDA science should ensure that statistical methods and acceptable criteria required to make comparisons

are demonstrated to be relevant and appropriate for the equivalence attribute being tested.

As you have already noted, there were several product-specific guidances presented, published, as well as articles presented. So we hope that FDA will continue to push this forward with their research and with their activities. That's all. Thank you.

DR. LIONBERGER: For the panelists, we do have a minute or two for questions. Do any panel members have any questions for the speaker?

DR. COOPER I'm Andrew Cooper from Mylan Global Respiratory Group. We've seen in the research priorities the use of clinical equivalence studies OINDPs is a very lengthy consideration. It's a big topic. And clearly, there's a priority to try and reduce that burden. But clearly, there was a lot of thinking that got to the position that we're now in, and it will clearly take some really significant new science to replace these studies.

I just wondered if you had any comments on the specific proposals for 2018 and how they might

move that on in the direction you've indicated in your presentation, and also what it will take to kind of validate those things as an alternative to clinical equivalence studies.

DR. PERI: Yeah. No, I think that's a good point. FDA has taken a lot of effort in publishing these guidance documents based on the PK in vitro as well as the PD studies that they have proposed. It does seem to indicate that some of these PD studies are taking a long time to do, and some of the companies obviously have succeeded and provided information to the FDA.

I think the FDA has a lot of information at this point to be able to do some modeling or perhaps come to a conclusion, at least preliminarily, as to what parameters or what type of models could be published to link in vitro and in vivo to a certain extent that it does justice for the guidance document that is published.

DR. LIONBERGER: Thank you, Prasad. We'll definitely be able to continue this discussion during the panel section.

Our next external speaker is Professor Mike Roberts. He's probably the person who's traveled the farthest to come here.

So welcome, Mike, and thank you for coming.

Presentation - Michael Roberts

DR. ROBERTS: Thank you, Rob.

Good morning, everybody. It's a pleasure to be here. I want to say from the outset that this is my view; it's not those of the FDA. I thought I should say that up front. I'm going to talk about skin. I've got a number of slides. I'm going to go through them very quickly, so I hope you'll bear with me while I do that.

The first thing I need tO point out is that topical products vary quite a lot in terms of what they consist of, and within those products, there may be a whole heap of other excipients and ingredients. But one area I think we always have to think about is the patient or the consumer and how they react. We find that that patient response is a clear part of the response as well as the actual efficacy of the product, and these

differences, when do they matter and when [sic].

One simple example, if we had to apply a generic product to the skin, does it actually go on as easily as the innovator, and in fact, what are the rheological differences that we need to have to actually compare that to being perceptible from the patient perspective. That's why the questions, in fact, we don't know the answer to quite yet.

I'm trained as a clinical pharmacist originally, so I want to give you an example of one which shows that this is an important area. This was a patient that came into our hospital for anal fissures and decided the treatment was in fact nitroglycerine ointment. And the surgeon decided this was too strong for the patient and asked if the pharmacy could dilute it.

The pharmacy did, and had the worst ever headache this patient could dream of. And the reason was they diluted this particular ointment with petrolatum, was inert, and should be perfect. The reality is that nitroglycerine ointment has lactose in it as well. It also has lanolin, both

which can actually increase the solubility or also reduce the availability of nitroglycerin, and that's why this happened. It's actually a lack of understanding of what the excipients are doing in terms of that formulation. So the take-home message, the excipient is important.

Another example that we'll be looking at with FDA has been a comparison of an acyclovir product, which is a Zovirax product, compared to one from Austria, which is acyclovir 1A. You can see there hae lots of variations, but two particular ones are propylene glycol and water. In terms of metamorphosis -- can I call it the proposed generic because it's not a generic -- actually has a faster evaporation rate. We can evaluate this with in vitro skin permeation test, which is a Franz cell which has some skin immersed in it, and we have a donor and we have receptor. The results we see for this is in fact the Zovirax product is much better. And the reason purely is the proplylene glycol is a much higher content and this is a penetration enhancer.

Another example, which is in fact one from Tom Franz and Paul Lehmann was one dealing with a compound called Diprolene and they're trying to find out how can we make a generic equivalent to the originator, so this was a prospective generic product. I looked at all the different types of -- at first I found that they could not get equivalence just using petrolatum on the market, so they looked at various petrolatums out there, and they found there was one petrolatum which gave a release profile similar to the original generic, identical release. However, if I put this into an IVPT, there are very big differences. Clearly, a petrolatum had an ingredient, which was an enhancer, which gave initial rapid release, so those two profiles are not equivalent.

Another example from a literature, which I think was interesting, is looking at the use of some of these generics and innovators, but this case was looking at the innovator applied to acne vulgaris. What I want you to look at is the overall and the adolescent results, but look

particularly at the placebo effect. You see the placebo effect is quite high, and in fact, in my experience, that can be as high as 60 percent of response for some topical products, particularly for the analgesics.

So there's clearly an age-related effect going on here for the placebo effect that we have to recognize. If you look at the severity of the disease, there's also a difference in the placebo but not actually in the response for the product. So the message here is we don't have to think just about the products, but also about what the placebo implications may be.

The other sort of point out I'd makde is that topical products are moving quite rapidly. We have a lifecycle process going on, and with patches, we've gone from reservoir up to now drugs and adhesive, a lot of these occurring with just complexity, ease of manufacturer, less failure, and easy to use.

When we hook up the generics, they actually have to follow on with these life cycles. So you

can see in the red, this is clear lifecycle, which is for the reservoir coming to an end. If you look at the generics, the generics are just starting. So in a sense starting on a new adventure in terms of our product, which has come to the end of a life cycle. This is a challenge. Somehow or other, we need to recognize when there are changes going on in terms of product development to lead to better products, and it becomes more challenging for generics with the time delays.

The other important thing for the skin is the heterogeneous organs. I sort of really realized maybe about 10 years ago, and I've worked in this area for a long time, that there were furrows and they could have an impact. But we don't really understand what they mean in terms of skin penetration. We also know that follicles are important, and in fact we've that since about the '40. So one simple example, if I try to apply a solution to the skin and I rub it in, I find it tends to remain fairly superficial. If however it's a nanoparticle and I massage it in, it can go

quite deep. So what that says is in fact the formulation matters but also how you apply it.

You can find the same thing in terms of rubbing in products. Here we're rubbing in that Austrian product again, and you'll get much better penetration if you rub it in. Partly that's due to change in the crystal size, but I think it's probably more becoming more intimate with the skin.

Another example is dispensing a product, so this is one looking at Zovirax tube and pump. So Zovirax in the UK can evolve by the tube and the pump. Here what you see is in fact that the tube gives you better profiles than the pump. Why is that? Well, what we find is when we look at the actual pump, it actually causes some dimethicone to come out, and that sort of leads to a change in rheology. And the other effect of that is in fact that you get this bioavailability. Another example for me is if you take up some sunscreen, if you apply it in a Franz cell, you can show the viscocity really can affect the penetration of that through the skin.

Now the [indiscernible], that doesn't occur. In fact, what occurs is as it gets more viscous, you probably get less penetration because the residual amount remaining on the skin probably causes more hydration. So some of the sort of theories we might apply in pharmaceutics don't always apply in practice in terms of actual use of products.

In terms of characterizing skin permeation, we're going through a bit of a change now. A lot of us work from the bottom-up approach or understand mechanistically how compounds go through the skin. And in fact we try and develop quite complex models or simple models to describe that. The other approach -- and this is something Amin will talk about later in his presentations, the top-down approach where we use much more population PK and understand variation in covariates between populations -- the reality we should bring the two together. So part of what we've been trying to do, to do that in terms of scaling up, particularly in vitro permeation to in vivo, and we carry out good

excellent correlations. But the danger we have is in trying to use these extraordinary complex models for skin -- and many of these are hexahedron shapes and diffusion models. And as one of my mentors, Bob Scheuplein, made the comment in journal article, which I recently helped him sort of write, "We have lots of information, but these complicated models aren't always verifiable, and we have to recognize that issue."

So there's a key take-home message. This is the last slide. One is about the products and what they do. I think it's better off, as Brian Barry said, to be approximately right than precisely wrong. And the last thing we want to do is to create a monster out of something which in fact doesn't need to be created.

I think that we need to think about quality by design concepts and take this all the way through, for prospective generics to apply not only to the formulation of design but also to the in silico, in vitro, and in vivo testing. We must be critical reviewing and adopting findings, so I

just want give you two examples.

Does the formulation affect stratum corneum transport? So this is some of my early work on imaging, and I've chosen here sort of an extreme example. This is imaging beta-naphthol in the stratum corneum. You can see just that the beta-naphthol gets in these saturated solutions with water. If you add propylene glycol, you can markedly enhance the amount of beta-naphthol that's in the lipids. But, if the solvent delipidizes the skin, affects that corneocyte envelope, then you can actually see the beta-naphthol goes inside those corneocytes. So you end up with a much more complex relationship than you think.

In terms of IVPT, this is some work done by my colleague, Jurgen Lademann in Germany. He did some work both in terms of in vitro open hair follicles and closed hair follicles, as well as in vivo. If you look at the data here, in vivo looks fantastically good and the in vitro looks terrible. You can never ever get an in vitro/in vivo correlation.

If you go and read the fine literature, fine details of what he's done, he actually used a full thickness skin. And a full thickness skin has no blood flow. The second point I'll make is how do we get from the site of action -- this is my arm withmicrodialysis -- to that person's face? We might apply things to the lip, but we normally assay things in the arm with microdialysis or the leg with microdialysis, or in fact use abdominal skin for IVPT.

We don't know too much yet about what occurs in terms of individual target sites, and we also haven't used the physiology of individuals very well. So here we can see there are differences in the stratum corneum thickness for this particular individual between the forearm, palm, and leg. And this will then in turn lead to massive variations in absorption.

I just want to make the point that sometimes the individual variability might in fact be greater than variation between sites, and you can see this here for the thickness for these various sites.

And my last slide is really to point out that we sometimes are measuring the wrong thing. So here we're measuring the dermal site for microdialysis, a long way away from the target site. Stratum corneum stripping is actually not really interested where the target sites are.

So if you look at the depth profiles, you see the dermal microdialysis and the OFM can be a long way away from where the levels are going to be measured at, say, 50 to 100 microns below the surface of the skin. And you've almost got a 50-fold variation in the levels here. We have to recognize local events clearance. To me, the holy grail, however, is what is going to be the drug product's skin sensorial interactions, and that is in fact where I think we have to go.

So thank you. I just want to reiterate, these are my views, not the FDA's.

DR. LIONBERGER: Thank you.

(Applause.)

DR. LIONBERGER: Our final speaker before the break is Guenther Hochhaus, who will be

talking, again, on inhalation products.

Welcome, Guenther.

Presentation - Guenther Hochhaus

DR. HOCHHAUS: Thanks, Rob.

What I would like to do is to present some work as well as some thoughts about the process of how we could streamline the approval off inhalation drugs. The work that I'm going to present is actually in collaboration with the VCU, Virginia Commonwealth University, Mike Hindle; University of Bath, Rob Price and Jag Shur; and I also want to mention that a significant portion of the work was done again by my colleague, Jurgen Bulitta, who's actually PI on that study. The disclaimer, you can read through.

So we already talked about the problem. The problem is that for inhalation drugs, we put the drug into the lung, and as consequence, some people say that blood concentration time profiles are not relevant. So the desire is that the FDA recommends a weight of evidence approach in vitro studies, pharmacokinetic studies to look at the systemic

safety, and then clinical studies to show the local equivalency. The clinical studies are for quite a number of those drugs a problem because there's hardly any dose response available and so on. So we all know that problem.

Our hypothesis was when we started this work was that in vitro tests and PK actually should be sufficient for at least slowly dissolving corticosteroids to test bioequivalence. I'm just going to show you some of the results and then also some questions, as well as the need for some potential studies, at least that's my personal view.

The studies that I present here, those are all preliminary studies, and what we tried to do is we tried to formulate three DPI formulations of fluticasone proprionate. All of those three formulations were identical with respect to the API particle size. All those formulations used actually the same bottle of the API. They differed in lactose fines, and the goal was to come up with formulations that differed in MMAD, and hopefully

this change in MMAD would reside in differences in the central peripheral ratio. And that was the main question that we asked, can PK identify differences in the central/peripheral ratio because dose and pulmonary residence time, I think everybody will accept that PK can identify differences.

So we assessed those formulations through in vitro studies. We looked at the PK and analyzed them through traditional noncompartmental analysis as well as compartmental analysis with pop-PK.

Here are some studies that we did that looked at the in vitro behavior. We performed quite a number of studies together with Mike Hindle, looking at time to identify potential differences in the ex-throat dose. So that would be the in vitro equivalent for the pulmonary available dose. And what Mike Hindle found also with our formulations here is that depending on what kind of throat you use, the differences can be significant. They are not only valid but also relative differences in the dose levels. So

sometimes they were almost similar and in some other throats they differed. So I think there needs to be some more work done to identify potential standard throats or maybe a collection of throats that should be used.

Here are the results of the cascade impactor studies. I think in those kinds of cascade impactor profiles, there could be quite a bit of information involved. But the problem right now is -- and you see here our formulation A or F17 seems to be having smaller doses depositing at higher stages. The problem right now is that there is no statistical test right now recommended by the FDA to probe for potential differences. At the same time also, there are no criteria that would give us -- some acceptance criteria.

So I think there should be still some work done to come up with statistical tests that are feasible to do and provide information about the potential differences in the shape of those cascade impactor profiles, because as I said, I believe there's quite a bit of information in those

profiles, and there's also the potential of in vitro/in vivo correlations with those kind of tests.

If you look at those profiles here, what we can see is, for example, that for formulation A or F17, it looks like the deposition is very, very similar to the other two at lower stage numbers, but that formulation A differs significantly in the deposition on stages 4 and 7. So if there is an in vitro/in vivo correlation, then one could maybe hypothesize that our formulation A might deposit less drug into the peripheral areas.

Another in vitro test that we looked at is the dissolution rate, and that was a little bit surprising because as I said, the API batches were identical. Both the three formulations only differed in lactose fines, but nevertheless, the dissolution profiles differed, and it was of interest to find out whether there might be an in vitro/in vivo correlation with respect to the dissolution rates and the absorption rates.

There are quite a number of projects that

was funded by the FDA with respect to the methods of testing dissolution rates, and I believe we are right now at a point where one should make a decision, okay, what could be a feasible dissolution method; can the FDA recommend a certain method that is most sensitive to potential differences?

We also could ask the question for what kind of compounds should those dissolution tests be performed? Certainly, it doesn't make a whole lot of sense for substances that dissolve relatively fast, so one could think about maybe coming up with some kind of BCS equivalent for inhalation drugs.

Certainly, we also need to test the potential differences in sensitivity of identifying different dissolution rates with the different methods. We can ask the question whether these statistical tests that are currently being used, whether they are adequate to make potential decisions and come up with acceptance criteria. And for that, we probably need to look also at in vitro/ in vivo correlations between dissolution

testing and absorption rates.

Here are the PK results. We tested three formulations, A, B and C, and formulation C was actually repeated, so that was a 4-way crossover. I don't want to go into those results too much, but what you see as really that the formulations differ in PK. We certainly can find differences in AUC, which would result in differences in the available dose of our formulations.

There was a significant difference also in the absorption rate. And formulation A, that is the one that also showed the slowest dissolution rate was absorbed the slowest. So there seems to be a correlation between dissolution behavior and absorption behavior. And of course the Cmax values were different, which could be due to differences in the absorption rate, differences in the available dose, but potentially also differences in the central-to-peripheral ratio.

We've also analyzed those data through compartmental analysis, and the result was the following. We were able to identify two absorption

processes, a fast and a slow one. And one could hypothesize there might be absorption from the central areas of the lung and the peripheral areas of the lung.

All three formulations were very, very similar in the absorption from the central lung, the slow absorption process. So one could hypothesize that actually the deposition in the central areas might be very, very similar, and that would actually go along quite well with our cascade impactor data.

Where the formulations differed were in the fast absorption process, and we saw that our formulation A, which had the larger MMAD, also resulted in a smaller dose deposited in the peripheral area as suggested by our compartmental analysis, but also was somewhat absorbed somewhat slower from this site. So what you see is really that our PK data correlated quite well with our in vitro data.

So could we now say that PK truly, at least for our drug, fluticasone propionate, would be

sufficient to describe the pulmonary fate? And pulmonary fate would mean dose absorption rate and central-to-peripheral ratio. At least our PK studies with using compartmental analysis seems to suggest that. Compartmental analysis and standard bioequivalence assessment are two totally different things. And maybe one has to think about using compartmental models for those kind of relatively complex questions and further test whether those compartmental pop-PK approaches might actually give us information about the fate of a drug in the lung with respect to central-to-peripheral ratios, and that might be some future work.

So if I want to summarize this now, certainly we should develop easy-to-use validated statistical tests for the cascade impactor studies. We should make a decision on dissolution tests. And for compounds like fluticasone propionate, I really would recommend to see whether pop-PK approaches are available in general for let's say slowly-dissolving drugs, and to test that, and maybe one could use this also for regulatory

decision-making together with the standard non-compartmental analysis.

With that, I would like to close. Again, Jurgen Bolitta, who's the PI of the study, was very, very helpful in performing the clinical studies. Postdocs and students are involved, University of Bath and VCU, and then also the folks from FDA who were really very, very helpful of trying to keep us on track. Thank you very much.

(Applause.)

DR. LIONBERGER: Thank you, Guenther.

So now we'll take a 15-minute break, and we'll return at approximately 10:25, so thank you very much. And remember the most important thing you can do during the break, order your lunch.

(Whereupon, at 10:09 a.m., a recess was taken.)

Public Comment Period

DR. LIONBERGER: We are ready to begin the public hearing part of the meeting presentation. We have five presenters who will present in this section. Our first presenter is Jim Polli from the

University of Maryland.

Welcome, Jim.

DR. POLLI: Thank you. My name is Jim Polli. I'm from the University of Maryland. I appreciate being able to be with you this morning. What I'd like to talk about is challenges in BCS-based biowaivers. There obviously has been tremendous progress in the last 20 years that the FDA has led, but just pointing out, there are probably some additional topics. And as you know, this is an ICH topic also.

This is the front of the December 2017 filed BCS guidance, a significant upgrade since the previous final guidance. There was a reference early in the morning to an October FDA workshop. This actually a slide largely taken from that referring to BCS class 3 research path forward. And in red, I just want to emphasize two things from this particular slide, quantifying excipient interactions with transporters and also testing via perspective in vivo Studies. Then just some additional comments, the new final guidance has

comments about two or more drugs that is fixed drug combinations, and also just comment very briefly later on about the utility of literature data; for example, how do you assess whether their data is good. These are two topics that seem to come up.

Just a little bit about the final guidance. For BCS class 1, which has been in effect for many, many years now, in general, it comments, many in general excipients in the FDA approved IR solid dosage forms will not affect drug absorption. There's a lot of missing text there, but I think that's the overall spirit of that statement when excipients are used in a common fashion. It says for BCS class 3, unike for BCS class 1 products, BCS class 3 test products must contain the same excipients as the reference product. The competition of the test product must be qualitatively the same and should be quantitatively very similar to the reference products, so sort of Q1/Q2. Qualitative, very similar, includes, and then there's a description of what that means. And it might remind one of SUPAC type of situations.

Here's just an example of comparing test and reference products, this particular product being lamotrigine immediate-release tablets. And not surprisingly, they're not identical. There are some differences in lactose there. The generic also has some additional components listed at the bottom.

I think as already has been alluded to, biowaivers have many advantages, reducing subject exposure to drugs, resources, arguably also a more definitive way to make assessments. So the question is when should biowaivers be applied to less risky drugs, but of course what are those, what does that mean? And of course, the BCS provides a framework for that.

Here's a somewhat older publication but I think still qualitatively very representative of today in terms of those large number of class 1 drugs and large number of class 3 drugs. More recently, actually quite recently, there was a paper on molecular pharmaceutics actually from FDA authors. I want to say it was around October or

November of 2017. And just some additional comments just sort of reiterating the large effect the BCS seems to have.

In the first quarter of last year, there was four BCS, NDA, or ANDA applications, and then in that same quarter, there were 26 ANDA approvals or tentative approval. So it seems like there's a big effect of the BCS. One Achilles heel, though, particularly with regard to this newer topic of BCS class 3 biowaivers concerns, excipients. And as we've heard this morning, excipients can be important.

The FDA funded a study that we did at Maryland several years ago. This publication was from a couple of years ago, 2016. And the title I think summarizes the main results, lack of in vivo impact of common excipients on oral drug absorption of BCS class 3 drugs, cimetidine and acyclovir.

Just some details, there were two studies, study 1 and study 2, study 1 actually composed of two studies, one involving cimetidine and one involving acyclovir as example BCS class 3 drugs,

in total examining 14 different excipients. Here's sort of an illustration of that. Very briefly, there were two 4-way crossover studies in healthy volunteers, one involving cimetidine, one involving acyclovir, and collectively 14 excipients were studied.

Because of some Cmax issues, we probably pushed the envelope too much with regard to HPMC as well as magnesium stearate. We also had overlubricating with magnesium stearate by virtue of how it was, study 2, which resolved some issues. And then the final conclusions are sort of mapped out here. There are 12 excipients here where there was just very large amounts of excipients employed and there was no bioequivalence issues. One formulation that included microcrystalline cellulose and HPMC didn't quite hit Cmax, so not able to say anything other than what's in the draft guidance at that time, which was Q1/Q2.

Conclusions from that study, 12 out of the 14 were found to be sort of non-problematic. We commented that it might be possible for other BCS

class 3 drugs that have properties that differ from cimetidine and acyclovir could theoretically pose some sort of problem. And in that context, we were kind of emphasizing just a focus on transporter type issues.

So this is sort of the issues, is this really a concern or not with regard to an excipient modulating drug absorption of a class 3 drug vis a vis some sort of transporter-mediated interaction? And there was a paper quickly that came out after the publication of that article, and then we responded. And the nature of the article was that the results from that study should not be extrapolated to other drugs. So very common criticism is can you generalize beyond the drugs that were actually studied?

I guess the good news is there are certainly a lot of tools available that have been developed over the last several decades with regard to examining transporter type of interactions and anticipating drug-drug interactions. In fact, the FDA has a -- I think it was last fall, last

December or so -- a reformatted and updated metabolism transporter drug-drug interaction guidance so things of that sort could be applied.

I guess the only last two things I would like to say is just comments about two or more drugs. The new guidance does talk about, very briefly, fixed-drug combinations. I guess my comment would be I think people could read that, it's very well written, but people could come up with different designs to try to analyze it -- to try to come up with an answer to that question.

There's still this issue of utility of the literature data, so the guidance continues to identify that there are -- sometimes it needs to rely on more than one data source. Some drugs that are absolute bioavailability is not cleanly known. So this is still kind of maybe another continuing topic in the BCS area about how to go about assessing whether data is good. Thank you very much.

(Applause.)

DR. LIONBERGER: All right. There's time

for one or two clarifying questions.

(No response.)

DR. LIONBERGER: So I have one for you on BCS class 3 drugs. What about the other aspect of the recommendations and the guidance, very rapid dissolution? Any sense of the importance of that or that being a barrier to widespread use of BCS class 3 waivers, having to dissolve completely in 15 minutes?

DR. POLLI: I don't know of any systemic study. One relative change over the last couple of years that probably gets the most attention is 500 versus 900 mLs. Actually, I haven't really seen a systematic study of the importance of that. Arguably it's not too important. But that's not a topic that I hear a whole lot about. I haven't quite studied that as far as concern about the need for very rapid dissolution. There might be opportunity to liberalize that given what's known about gastric emptying and things of that sort being potentially more rate limiting than even very rapid dissolution.

DR. LIONBERGER: Thank you.

Our next speaker in the public comment period is Sid Bhoopathy from Absorption Systems.

DR. BHOOPATHY: Good morning, and thank you for this opportunity. I'll be talking about the importance of bioassays for establishing equivalence, which we believe can link the API and the formulation to their biological effect. All of us here have seen these types of pictures, the slowdown in approvals being attributed to these more challenging, difficult types of products, and that's because it is primarily the in vivo barrier, which could be a clinical endpoint study or a site of action PK study.

Exceptions used to exist, which were fewer and far between. They were API specific or RLD presentation type specific, or PD characteristics specific. But again, with the advent of new approaches, new technologies, the in vitro bucket has continued to grow, essentially with the coming together of this in vitro characterization-based equivalence, where essentially you're matching the

input, the API, the excipients. You're optimizing the process so that you have this in a controlled, reproducible type of manner, and then you measure the output, which is your formulation function characterization.

But even with the advent of this approach, it has its limitations, and several speakers have touched upon it in the earlier sessions. Some of the questions that come to mind are which attributes to measure, the in vivo link. How do you identify the key factors that impact bioavailability at the site of action, and if you do identify these key factors, are they all in the same plane or is there a hierarchy in terms of relevance? How to perform these studies? Knowledge and experiences coming together, but there are still several open-ended type of questions. And many times, we're trying to track down a difference that may or may not be relevant. Does it carry forward as you start thinking biorelevance. But because we're uncertain in terms of how much difference is critical, the process

optimization becomes more of an open-ended process, and it's a vicious cycle.

All of these challenges are exacerbated when you have complex or multifactorial or layered biology, or when you have more challenging APIs, multiphasic formulations and so on. And a constraint of this approach currently is that it is only possible to think along these lines when you have that Q1/Q2 match.

So the thinking could be, well, again, this continues along the path of the opportunity for innovation and sort of in vitro characterization-based equivalence, having to carry so much of the therapeutic equivalence burden, you can maybe bridge that with these integrated functional type of bioassays.

The questions being asked could be, well, how do I make it closer to the target physiological action? Are there other models that could maybe study the interaction between the site of action and the formulation along the lines of a surrogate PKPD? Like what does the site of action do to the

formulation and what does the formulation in return do to the site of action?

Such PK assays could include interaction assays and accumulation assays. A formulation to the site of action could include some type of enzyme inhibition or up-regulation assays, healing biomarkers that are able to quantify the cure.

This is how maybe a modified paradigm could look like, where you still of course focus on the sameness of the input. The process is controlled, but instead of relying on the Q3 box, which is solely formulation function, expand it to an augmented Q3 by bringing in such biorelevant tools that are selective, sensitive, and reproducible.

The development of such models takes on a very logical paradigm. We first have to understand the endpoints that matter, and then start putting methodologies and modes of measurements that are relevant to that endpoint. We optimize the radius finite assay parameters; adapt as relevant a physiological condition as possible; qualify to ask the question is this validatable, which also means

that it is probably better to work with multiple assays that are looking at the same endpoint because some of them may be too noisy, variable, less validatable and then establish the key parameters such as sensitivity, reproducibility, can it discriminate. And once you establish that this is validatable, move forward with the validation eventually to the quantitative comparison of the RLD and the test formulations.

The next few slides are just some examples of bioassays that we have worked on that demonstrate these types of advantages where they can complement the knowledge that can be derived from formulation function characterization. So here's an example of an integrated effect assay, so comparative physical-chemical characterization; some examples of what developers normally look at in these different complex routes of administration, local GI, ophthalmic topical, but here is an integrated assay which assesses the combined effect of changes to viscosity, dissolution, and specific gravity. This assay is

essentially looking at enzyme inhibition, change in percent activity remaining with increasing drug product concentrations. The assay has been shown to be sensitive, selective to formulation variance, and also specific, and therefore can be used for these types of conclusions.

A second example where confirmation of the same endpoint using a different assay or methodology, maybe one that is even closer to the target physiological action. In this instance, the endpoint that is being measured is impediment of a noxious agent to the site of action of the disease state. Impediment could imply a multiplicity of actions. And then as you attempt to break it down, this could be association based. This could be delay of diffusion based. So as you put these combined bioassays together that are looking at the same endpoint but in two different directions, these outcomes become complementary, and this combined selectivity strengthens the assurance of your overall conclusions.

Also, bioassays not only have the ability to

quantify a single formulation property, but because they have the ability to study integrated effects, you're able to evaluate multifaceted formulation related effect mechanisms. So in this example, if again at the site of action, the formulation and the site of action have had early interactions, and intermediate, and extended, and all of these are relevant to what occurs between two doses of the drug product, bioassays become a more elegant and a more relevant way of studying such interactions.

If a bioassay has ability to study the integrated effect, has the ability to look at the same endpoint through multiple meaningful measurements, and you're able to demonstrate greater relevance of biocontext, and if it is selective to formulation compositional differences, it is an opportunity to maybe mitigate Q2 differences, to ask and answer the question do these matter, do these carry forward as you're establishing equivalence.

So one could maybe use this type of thinking to construct a zone of no bioimpact with Q2

differences. And this is the point illustrated here with three different assays that track the multiple postulated mechanisms of the product between doses of the drug product.

This is my conclusion slide. Clinical studies gave us the opportunity to innovate. In vitro characterization-based equivalence is a fantastic step forward, but the success is based on Q1, Q2, Q3 being achieved, which can sometimes limit the utility. If we add one more layer to this and start thinking along the lines of bringing together these integrated assays, then maybe development can be independent of the product-specific guidance, and you can take the initiative to move things forward.

This is along the lines of the totality of evidence approach that is a possibility of wider product development applicability and the possibility to overcome Q2 and Q3 differences. Thank you.

(Applause.)

DR. LIONBERGER: Thank you very much.

Our next speaker is Vatsala Naageshwaran.

MS. NAAGESHWARAN: Thank you, good morning, for this opportunity to speak about nonclinical models that have IVIVC and help to establish and support bioequivalence for complex ophthalmic products. Bioequivalence for complex ophthalmic products is challenging to establish because pharmaceutical equivalence need not translate to therapeutic equivalence. Q3 categorization to show structural similarity is applicable to a subset of products indicated by the FDA, however, the sufficiency of this categorization to establish bioequivalence still remains in question.

The reason is there is some uncertainty around the testing methodologies, which impacts the results. There is no defined criteria for these comparative assessments. Importantly, it lacks correlation to critical in vivo parameters like precorneal dynamics, and the rate and extent of drug absorption and distribution to target sites. It's an important point to ask the question as to whether these testing measures were used that led

to the subsequent approval of the RLD because if not, therapeutic equivalence, efficacy and safety cannot really be assured based on this testing alone.

So formulations which have similar Q3 parameters need not always have the same permeability or PK profile. And this isn't surprising because you can link CQA to CPP, but the link of CQA to in vivo effects is still not well defined. So integrating permeability, ocular PKPD, preclinical PD, and modeling this to integrate formulation factors as well as the dissolution characteristics of these products can enable an evaluation of the sensitivity of these parameters in an extrapolation to human ocular bioavailability and efficacy.

The summary basis of approval of RLD products is really contingent and based on such scientific models which mimic the conditions of drug administration within a physiological context. So you have a scientific model like IVPT, which has a multifactorial output that gives you net flux

that provides association or selective retention within ocular tissues; the partitioning of a product between what is permeated into the aqueous humor versus what may be associated still with the cornea; the nonclinical PK, which gives you the distribution in different ocular compartments; and the PD, which is representative of different disease phenotypes. These can be integrated to provide this confirmation that enables approval of RLD, and this is corroborated by the efficacy that we see in the clinic.

So IVPT is a model that we have established in our lab for over a decade, and it utilizes freshly excised corneal and conjunctival tissue that is obtained from rabbits, albino as well as a pigmented strain. And we have extensively characterized and validated this to look at the morphology, to look at the distribution of transporter proteins, esterase expression, the permeability of over 20 model compounds, the effect of strain, and establish numerous correlations in vitro to in vivo within the rabbit cornea

permeability to aqueous humor concentrations; corneal rabbit to corneal human, and also to the published literature data.

So if we look at some of the characteristics of this validation, what went into it when you look at the ability of this model to discriminate compounds based on their chemical class, and you look at drug products like betaxolol, which is lipophilic in its high corneal permeability versus brinzolamide, which has a 4- to 5-fold higher conjunctival permeability compared to the cornea. You see that you have the ability to social performance across a very wide dynamic range. So both corneal and conjunctival tissue, permeability has been assessed for these different model compounds. The reproducibility of this model has been established using reference standards, reference markers that represent bookends in terms of permeability characteristics.

The success of delivery strategies of prodrugs, ester prodrugs like dexamethasone acetate or latanoprost, can be really evidenced from this

type of model because you will see the higher permeability of the active metabolite following the administration of the prodrug. And it's higher in the cornea than the conjunctiva, rightly so, because the strategy here is to establish high local concentrations and reduce that systemic exposure through the conjunctival route; so a model that has been validated, established for its sensitivity, selectivity, and reproducibility for formulations for many, many brand products that can be utilized, again because of the established IVIVC.

So again, further on this, the comparison between human and rabbit cornea, which is actually stronger in terms, for example, with reference to esterase expression compared to human corneal orbs, which are derived from stem cells, which were provided to us by the International Stem Cell Corporation. And the sensitivity of the model to pick up on these formulation differences as illustrated in this example of this bimatoprost formulation that we were evaluating to BAK-free

formulations compared to the reference product, which was Lumigan. And as you know, this is the .01 percent, which has a 4-fold higher concentration of BAK.

BAK is known to increase the transcorneal drug penetration by modifying the tight junction morphology, and that's what is evident in IVPT results where you see the flux of atenolol, which is a paracellular marker, is above the threshold for Lumigan and it's within the acceptable levels for a formulation that doesn't have BAK, again corroborated by the clinical data that we see from the package insert that 12-month clinical study shows that the highest incidence is of conjunctival hyperemia in the patients who received the topical application of this product.

So a few examples of, again, how IVPT can be very sensitive and discriminatory using dexamethasone as an example here, because we have a couple of products within this product family. Here is a comparison Tobradex versus Maxidex. Both have the same concentration of dexamethasone, which

is the active ingredient, but when you actually look at the flux profile, Maxidex has a lower flux, or per parent, compared to the Tobradex until you actually look at what is the solubilized drug in the donor compartment, and then when you normalize the flux to the actual soluble concentrations, these become equivalent. So you see this almost 2-fold higher soluble concentrations of dexamethasone from Tobradex compared to Maxidex, which is supported by the posology of the product because you have to administer Maxidex several times a day compared to Tobradex.

This is further seen in this very sort of classic comparison of Tobradex versus was Tobradex ST. The ST product, of course, as we all know was developed in order to reduce the amount of dexamethasone, so it's 50 percent lower than Tobradex, and yet it has the xantham gum that enhances the retention on the cornea and thereby is apparently supposed to deliver the same exposure, ocular exposure, for the effect.

So what we see here in the IVPT model is

that ST is actually disproportionately higher when you consider the load of active ingredient concentration of dexamethasone within this product. But again, this becomes equal once you start identifying what is the free drug that is solubilized to begin with. And when you do that, you actually see these become equivalent, and ST even a little bit higher in terms of flux, which again correlates with the association with the cornea, which is what the formulation is intended to do, which is form that depo and then enable comparable exposure.

So what we've been trying to do is to look at the preclinical PK and to look at those critical compartments, the tears, the aqueous humor, the cornea, and to look at the Cmax and the AUC profiles. And what we see is no significant difference in the Cmax or the AUC between Tobradex and Tobradex ST, which is exactly what the human data also indicates, which is why this ST product was able to be favorably launched.

So in summary -- this is my last slide -- I

just want to emphasize the criticality of bioassays for the confirmation of equivalence because they help to link API and formulation to the biological effect. And unlike the Q3 tests, which are discrete, you're able to evaluate the combined effect within a physiological context, taking into account the precorneal dynamics, the multiple target tissues, the complex processes that are constantly changing to achieve equilibrium. And you're able to most importantly provide scientific evidence that is congruent with the requirements for RLD approval. So this will then support the expected equivalence in human efficacy, providing confidence to clinicians, patients, and regulators. Thank you very much.

(Applause.)

DR. LIONBERGER: Thank you. Our next speaker is Stephen Hoag from the University of Maryland.

DR. HOAG: Hello. Thank you for giving me the opportunity to speak to you today. I'm going to quickly talk about my feelings based on my

experience of some of the key needs in research in the area of excipients, And I'll give some examples of these and talk about that.

Today we spent a lot of time talking about how excipients can affect bioavailability and bioequivalence, and all that type of thing, but I also remind you that excipients have a lot of impact on manufacturability, stability, drug delivery attributes, which we've already emphasized, and other properties. So we need to keep a broad thought about all of these other attributes because things like stability can be just as important as delivery.

When we look at excipients, this will kind of give you an idea, they have a key impact on the quality of a product. Here's kind of a manufacturing chain where we have the process inputs, which chemical engineers love to study. And we also have the material inputs, the material science attributes. In my opinion, and based on my experience, the material science is something that needs a lot more work. Understanding how these

things influence product quality is something that's really needed, and this is particularly true in the generics now. When look at a generic company, they have to produce a product that matches the RLD, but they also have to do that in an environment where perhaps they're looking at a patent of the innovator that says composition comprising lipophilic materials in such and such composition. So they have to come up with a formulation that has the same release rate but has different excipients and things. So this can be challenging, so people really need to understand how these excipients can behave and affect this.

This slide shows you what I feel is a lot of the big problems that need fundamental research. When you look at excipient, you could look at the molecular level. You could look at TG molecular weight, degree of substitution, origin, all of these different properties. You can look at the particle going up in size. You can look at a volume element, what is the bulk properties, what are the flow properties. And relating these

various attributes to then bioavailability or stability or manufacturability is something that is not well understood. We have general ideas, but there's very, very few first principles. So I think this is something that needs to be looked at.

In addition to this, poor understanding of attributes. Obviously, we have some basic ideas like particle size and things, but there's also a lack of standardization of measurement, so comparing things. And sometimes when you measure things, it will be impossible to completely standardize the measurements just because the nature of the differences in equipment, but understanding how these relate to each other.

One way that I think is a good way to do this is to put things in databases, start to have material databases. I know that the FDA does have databases, and this is one thing that we've developed. But I think some of these databases, if you want to get down to the next level of nuance, you need to be aware of the variability in excipient. So if you look at some of these

databases, they'll say here's the bulk property and they'll give you the average density of glycerol or something, but if you want to go to the next level and where do product failures come from, and where do recalls come from, and where does stability problems come from, then you need to start capturing in these databases the variability in that. That's somewhat in C of A of materials, but you know, unless you're like Pfizer, has done studies and has five years of C of A's in their database, it would be nice for the generics and all the pharmaceutical companies have access to these types of things. So that's one thing.

Then for some of the specific dosage forms, as I said, our knowledge of excipients comes from experience, empirical observations, and things like magnesium stearate. Through experience, we know how to blend that where you blend that at the end of the process and various types of things, and we're all aware of problems that can occur with mag stearate blending on scale up and things.

But when you look at other dosage forms,

because you don't have first principles, how that extrapolates to these other situations can be a difficult. And in particular, I think some areas that would benefit a lot from research, like pediatric dosage forms, taste masking, how do you evaluate the taste and also associate with that some of the excipients in pediatric dosage forms. I know the EU and NIH has done some stuff with the database, but what is the toxicity of those?

In particular, we have neonates and infants and how do you evaluate it? I was just talking to one of my colleagues, who's a pediatric pharmacist, and says it's very common for an infant to be taking antibiotics and they should all be cleared up, and then they're recurring coming in because it's very difficult to give drugs to these patients, and in the middle of the night or whatever, the caregiver says I'll just forget this, and that leads to resistant strains and things.

So I think that's one thing, and also working on ways of evaluating these. Also, for pediatric patients, it's the whole palatability,

the texture, all of those things need to be considered. Another area that I think is very important is in the low solubility drug excipient interactions, that glassy state, how do we maintain that, and all those types of things.

A third area that I think is very important is abuse-deterrent formulations. I think some of the key issues is how do you evaluate the excipients, how do you evaluate the performance? And one of the key issues that I think needs more research is what is the level of effort. Like for example, I can guarantee you that I could somehow get around any product on the market if I had my laboratory skills. But what is realistic, sometimes you hear people say, well, we'll take this drug, and we'll put it in there, and three days later we'll do an extract and potentially abuse that. But is that something realistic that an abuser would do? So some of that needs to be done.

Then also, I think another big area of excipients that's much needed research is in

biotech products. I think that one of the key issues looking at biotech products is stability. I think looking at, for example, what is the relationship between the drug, the API purity, and the biotech product stability.

Also, I was just at a conference where I saw 10,000 pictures of ribbons and modeling of the molecular proteins and things, but all of these models are done in liquids. And when you look at a lot of the things, lyophilization spray drying, a lot of the proteins are glasses when you lyophilize that. So I think looking at that modeling in that glassy state would really advance that because I find that a lot of the stability changes occur on storage, I mean, in terms of things like aggregation. So they're not just the process development but the storage. So I think that's a really needed area for biotechs.

Also as we just heard, for example, looking at transdermal products and things, what are the interactions between the excipients and the skin and things? Well, biotech products are expanding

in use, for example, ocular delivery and things. So that is something, looking at how those excipients interact with the physiology in the reference or context of biotech products.

This slide may be a little bit premature for this meeting, continuous manufacturing, because I'm not sure the generics do much continuous manufacturing. But I think some recent advances, the cost of continuous manufacturing, and also the generics changeover, the cleaning of the equipment has gotten much better. So it is my feeling that people should look at this because I think the generics will start to adopt this more quickly and stuff.

How do the excipients perform? We talked about mag stearate. We have a lot of ways that mag stearate can be done in the batch process, but how is that done in a continuous process? Because I think that the continuous manufacturing, because of its cost advantages, will be coming to the generic industry.

A final thing is approval of new excipients.

I started off talking about the context of coming up with formulations and getting around patents and things like that, so I think ways of improving the development of new excipients for the industry, and also this would help innovators, too.

(Applause.)

DR. LIONBERGER: Thank you very much.

Our next speaker is Gordon Amidon from the University of Michigan.

DR. AMIDON: Thank you for the opportunity to talk about some of the surprising results we've obtained in the past two years investigating oral delivery, oral bioequivalence, and oral product performance. I'm going to talk about technology. We want to develop a gastrointestinal simulator. Our current devices go back 50 years or more, so they haven't really been updated to modern technology. They haven't been updated to match what's going on in vivo, as I'll show you in humans.

This is a device that was developed by a generic company because they did a bioequivalence

trial that failed, and they want to know why. So that's a question actually we need a device for. I think of it as kind of the Phoenix rising out of the sun, from the ashes. So I'll talk about gastrointestinal processes, pH buffer, enteric coatings, a gastrointestinal simulator, some MRI work, and in vivo plasma variability.

So to predict gastrointestinal absorption, you need input. If you solve differential equations, you need an input function. And without the right input function, you're not predicting anything of value. So we need to know what the input function is.

Our project in the last two years has been to directly measure the gastrointestinal levels of drug and plasma levels simultaneously. So we want to measure what's going on. We want to determine what are the actual variables that are controlling oral product performance. So we put tubes into subjects. This is commonly done in gastroenterology. We want to replace it with MRI, and we're in the process of doing that now. We

sampled in four sitesa: stomach, duodenum, jejunum, and upper ileum. We usually got four sites, but not always. When you're working with human subjects, you don't always get samples. And we measured the motility showing in the computer screen on the right. We measure the contractile activity in the intestine simultaneously, continuously, and we measured gastrointestinal variables.

This is an example of the fasted state motility patterns, contractile patterns in the different regions from the stomach in the top, the top three of the stomach, and it propagates through the intestine. That's the migrating motility complex. It's been known in gastroenterology for 50 years. So this is measured by pressure contractions in the intestine.

The MMC, I'll show you, was the most important contributor to Cmax variation because we dose randomly the patient. The patient, the subject, is in one of these gastrointestinal states, and when we give them a dose in the fasted

state, it could be any place. So that's a random variable we have to account for. So I'm kind of curious, the correlation between Cmax and the predicted Cmax actually based on the MMC, the time to phase 3. I think that's shown here. The left curve shows the Cmax and the time to the MMC phase 3, the strong contracile activity, which I just showed you.

We also looked at the pH. we measured pH and the pH correlation. It's not quite as good, but then we can combine them in multiple regression. I'm not going to talk about the details in this seminar, but we can do a multiple regression with both motility and pH to explain what's going on.

Now, the first surprise for us was that ibuprofen, we give the RLD -- we use the RLD for Ibuprofen, and it's in the intestine for seven hours. You can see even in the stomach, duodenum and jejunum, you can see ibuprofen levels in the intestine for 7 hours. Wow. What's going on? Ibuprofen dissolves in 10 minutes with the USP

test. Of course, this is an OTC. I'll talk about enteric coding. But it dissolves in 10 minutes, in a minute. So clearly there's a problem with our USP tests; it's not in vivo relevant. In fact, it's wishful thinking I think. However, it dissolves much more slowly in bicarbonate, which is the physiological buffer, the in vivo buffer, the buffer in the gastrointestinal tract. Actually, the buffer capacity in USP fluid is about 20, 18.

I missed this slide. I sent this at night, so I obviously missed a slide when they asked for the slides. I missed a slide. The buffer capacity in the intestine is only 2, and the buffer capacity of the USP buffer is 20 or 18, so a much lower buffer capacity. And we published it. I probably have it in a later slide.

I want to talk about the important product is an enteric coated product with regard to oral performance. We looked at the Bayer, which is an OTC product of course, and it has little hearts on the bottle because it's recommended for everyone that's as old as me or younger for myocardial

infarction prevention and for brain ischemia, stroke. But it doesn't work, and we've known that for quite a while actually. In fact, just clinically, it's been shown -- here are two publications. One is in circulation, a recent publication in circulation showing drug resistance and pseudo resistance and unintended consequence of enteric coated aspirin. In other words, enteric coating doesn't work.

Another study in diabetic patients, actually the editorial here is, "Collapse of the Aspirin Empire." That's really misleading because it's not collapsed of the aspirin empire, it's the enteric coated aspirin that doesn't work. Aspirin works. Aspirin isolates the thromboxane and inhibits platelet aggregation. But the enteric coating doesn't release in vivo, so we actually studied that. I can't point I don't think, but the 5 millimolar bicarbonate -- in vivo bicarbonates 2 millimolar along the gastrointestinal tract. The curve at the very bottom, right on the X-axis is the dissolution rate of the enteric coated aspirin

and 5 millimolar buffer. It doesn't dissolve; well, it takes a long time, more than 240 minutes. That's what? Four hours, because the buffer capacity is so low. So we published that.

We're in the process of establishing an in vitro dissolution methodology, and we may have to use bicarbonate because that's the in vivo buffer. Of course that will be a nightmare for analytical chemists because it produces gas. Right? CO2. We worked out the bicarbonate buffer system, and in vivo is an open system, not a closed system. It's a little more complicated physical chemistry, and we worked that out, and we're in the process of preparing a publication to show that it's the concentration of bicarbonate that's important, not pH. The magic of the bicarbonate buffer is the counter ion disappears when carbonic acid -- when you get a neutralization of an acid by the bicarbonate ion, it produces Co2 and water, and they disappear. We don't have a counter ion to worry about. That's the magic of the bicarbonate buffer. That's why it's the in vivo buffer, at any

rate.

So we have published the initial studies from the past two years. This is a summary. We're continuing to work on various aspects of the gastrointestinal oral absorption modeling, but we've learned two important things. And then we're going on to studying MRI now. That's ongoing studies right now because while the intubation methodology is I think generally thought may be somewhat invasive, our subjects do come back, so it's not bad. In fact, this is a common gastroenterological technique, but we're developing the MRI technique, cross-validating it with the classical intubation method that gastroenterologists use. Then the MRI technique can be used in pediatrics. It can be used in patients. It's much more broadly applicable to locally-acting drugs, a set of drugs that we could study in the next year.

To summarize here, we've measured gastrointestinal mechanism, buffer capacity, and in particular the bicarbonate buffer, and it's much

lower. It's much lower than the USP buffer. We've shown that the enteric coated aspirin actually doesn't dissolve in an in vivo buffer, so we've got to look at the standards we're using for our products, particularly delayed-release products, and I think it's more general than just for enteric coated aspirin.

I think we dose randomly relative to the gastrointestinal motility, and I think we can measure that by MRI techniques. We are doing studies now where we can determine the MMC as well as the actual contractile activity by MRI at the University of Nottingham, a world center of MRI expertise.

I think we can ultimately reduce the variability in the bioequivalent studies and reduce the need for subjects, probably not reduce it to zero, but I think ultimately we can. I think that's going to take some time to replace in vivo studies with in vitro, but we're making progress, BCS class 1 for example. Ultimately, we'll capture this in an in vitro device and a gastrointestinal

simulator, which we will have working this summer.

I see the red light, so thank you very much.

DR. LIONBERGER: Thank you very much.

(Applause.)

Panel Discussion

DR. LIONBERGER: So now we'll be moving on to the panel discussion section of this morning. First, I'd like the panelists to go around and just briefly introduce themselves. We'll start with Mark on the end.

DR. RITTER: I'm Mark Ritter. I'm the associate director of the Division of Clinical Review in the Office of Generic Drugs.

DR. PERMUTT: Tom Permutt. I have a statistical policy group in the Office of Biostatistics.

DR. MEHTA: Mehul Mehta. I'm with the Office of Clinical Pharmacology, division director, Clin Pharm I.

DR. McNEIL: I'm am Scott McNeil. I run the nanotechnology characterization lab at the NCI.

DR. KIMBELL: My name is Julia Kimbell. I'm

an associate professor of research at University of North Carolina School of Medicine. I run a computational fluid dynamics lab for studying nasal uptake and deposition.

DR. HOCHHAUS: Guenther Hochhaus from the University of Florida.

DR. DUTCHER: I'm Sarah Dutcher. I'm an epidemiologist in the Office of Surveillance and Epidemiology.

DR. CRUZ: I'm Celia Cruz. I'm director of the Division of Product Quality and Research within the Office of Testing and Research within the Office of Pharmaceutical Quality.

DR. COOPER: I'm Andrew Cooper. I'm the head of analytical and material sciences within Mylan's global respiratory group.

DR. CHAZIN: I'm Howard Chazin. I'm the director of the clinical safety surveillance staff in the Office of Generic Drugs.

DR. UHL: Good morning. I'm Kathleen Uhl. I'm the director of the Office of Generic Drugs here at CDER.

DR. ROBERTS: Good morning. I'm Mike Roberts from down under, University of Queensland and South Australia.

DR. ROSTAMI: Amin Rostami from the University of Manchester, and also I am chief scientific officer for Certara.

DR. SCHWENDEMAN: My name is Steve Schwendeman. I am the chair of pharmaceutical sciences at the University of Michigan. I'm also the advanced material and drug delivery thrust leader of the Biointerfaces Institute at the University of Michigan.

DR. SEO: Paul Seo, director of Division of Biopharmaceutics in the Office of New Drug Products, Office of Pharmaceutical Quality.

DR. STEIN: I'm Steve Stein. I'm a scientist at 3M Drug Delivery Systems, focusing on pulmonary delivery.

DR. STRAUSS: David Strauss, director of the Division of Applied Regulatory Science, Office of Clinical Pharmacology, Office of Translational Sciences at FDA.

DR. SUN: Hi. I'm Zhigang Sun, and I'm VP of regulatory affairs at Sun pharmaceutical industry.

DR. TAMPAL: Hi. Nilufer Tampal. I'm in the Office of Bioequivalence, Office of Generic Drugs, and I'm the division director for Division of Bioequivalence III.

DR. TYNER: Hi. I'm Katherine Tyner. I'm the acting associate director for science in the Office of Pharmaceutical Quality.

DR. CRENTSIL: Hi. I'm Victor Crentsil. I'm the acting deputy director, Office of Drug Evaluation III, Office of New Drugs.

DR. LIONBERGER: I'd like to thank all our panelists for participating today. So again, our goal here is to obtain input into research priorities for generic drug development over the next year. So again, be thinking about that when you your comments. To begin the discussion -- again, we have about an hour for this discussion, so I'll try to move us from topic to topic and ask people to contribute in each area.

I want to start with the inhalation area. We heard presentations both from the generic industry and from Dr. Hochhaus about the next steps in the inhalation area. So open to begin comments and discussion on what we should do next in the inhalation bioequivalence area. What are the key challenges that we can do research on that would help availability of generic competition in that area.

DR. HOCHHAUS: I think the FDA has funded quite a number of studies right now that strengthen certain methodology: in vitro computational fluid dynamics; PK, which I think provides quite a bit of information that those kinds of tests together with PK can provide quite a bit of information. And I think the next step really would be to -- I mean we are almost at the finish line to do a couple of more studies to validate those approaches and compare them maybe with clinical studies for some of the drugs.

So what I would like to see are studies that finalize statistical tests for cascade impactor

studies. There are some methods available, but I think the FDA believes that they are somewhat too complex, and maybe there are ways of making them a little bit easier, either providing computer platforms that are easier to use or to develop similar statistical tests with similar properties.

DR. LIONBERGER: Can some of the members from the industry perhaps comment on the cascade impactor profile comparison aspects? Is there any aspect of that related to Guenther's comment that the industry representatives might want to comment on?

DR. STEIN: Certainly, cascade impactor profiles are crucial. It kind of comes down to how close is close enough, and obviously there's been good research on trying to develop statistical approaches. That is helpful and there are helpful publications. Ultimately, I think what really helped the industry is when it comes down to a guidance level where people understand what is acceptable.

DR. HOCHHAUS: I think those are studies

that need to be done to just come up with acceptance criteria that probably should be linked to in vivo performance also, so if one looks at in vitro/in vivo correlations and then from there comes up with acceptance criteria that makes sense.

DR. LIONBERGER: Zhigand?

DR. SUN: I think the same thing. I want to say when we compare to the cascading profiles, I think maybe, from the FDA perspective, we should really understand the RLDs' variability because in some cases, in the industry there's a lot of variability even in RLD or something, but maybe it's not for sure. Maybe the method is different. So I really want to have some standardized method and also have some publication regarding the RLD drugs about these kind of profiles. Thank you.

DR. COOPER: Yes. I think there are obviously a number of metrics that have been looked at and proposed for cascade impactor studies. I think it's reasonable that -- and I don't that it actually matters that much exactly what metric you use. So I think some standardization around that

would be helpful.

For me, the bigger issue with cascade impactor studies is just that there are so many different ways of doing them. We see a lot of work being done with inhalation profiles, with throat models, and how will those things interact. You can get a lot of very different results according to exactly how you do the experiment, and I don't think we're yet at the point that we've really nailed down what's the best way to do the experiment. And for me, that's more important actually than how you set the criteria and the results at the end.

DR. LIONBERGER: Guenther?

DR. HOCHHAUS: Yes. I fully agree. Mike Hindle did some studies with our formulations that I presented there, and that was really depending on what kind of throat you used. Those three formulations were almost equivalent up 2-fold difference in impactor size mass or ex-throat mass. So there's certainly some work that needs to be done to either come up with a standard throat that

kind of describes what's happening in PK studies with respect to the dose deposited or even with a combination of throats.

DR. LIONBERGER: Michael?

DR. ROBERTS: I just didn't pick up what actually happens in chronic obstructive airways disease or other respiratory conditions in terms of this generic bioequivalence? How much do we know in that space?

DR. UHL: Can I just follow up on that question then? Because we're trying to understand what our research priorities would be. So in the case of most of these inhalational products or a lot of BE, we would recommend that you do them in healthy volunteers. So you're advising the agency that it might be beneficial to do research in the area of patients with disease in order to demonstrate bioequivalence.

DR. ROBERTS: The question I have is I don't know what happens in terms of the disease state, whether the bioequivalence that you see in normal patients actually translate to those disease

states --

DR. UHL: Okay. Thank you.

DR. ROBERTS: -- particularly in the very severe cases.

DR. HOCHHAUS: Healthy volunteers are probably more sensitive because you have the whole lung where the drug can deposit, while in certain diseases, it's probably going to be the restricted to the more central areas. So if the performance of a generic and innovator are somewhat different, you probably can catch it easier, at least through PK studies, in healthy volunteers.

DR. ROBERTS: Is that an assumption or do you have proof?

DR. HOCHHAUS: There's somewhat of proof if you look at the -- at least there's indication that the central deposition in asthmatics is that more drug is being deposited in the central areas compared to healthy volunteers, where it is more spreaded. And those studies are based on -- I don't want to go -- maybe we can talk about it afterwards.

DR. ROSTAMI: But based on actually this response, you are basically admitting that we are looking for differences in healthy volunteers, which may not be actually relevant in the patient group.

DR. HOCHHAUS: Yes, but if those kinds of tests would prevent doing clinical studies, I would accept that.

DR. LIONBERGER: I think there's always a tradeoff between the sensitivity. In the bioequivalence, we often say the bioequivalence test is a sensitive comparison of the formulations. And if we show the formulations are the same, then they ought to be substitutable in a wider group of subjects.

So there's a sense that a sensitive maybe more sensitive test might still be a useful tool. But I think it is good. I think one of the reasons we've invested research in a lot of the modeling and simulation areas is to be able to through the modeling translate from one aspect to the other to say we've done a study in healthy subjects. What

would this tell us about a different patient population that you can't necessarily do a full set of routine studies in?

We have a comment from the audience.

MALE AUDIENCE MEMBER: Youen Wita from the University of Florida. I was wondering if given the models, which Dr. Hochhaus showed earlier today, is there an opportunity we can further leverage perhaps industry data sets or data sets available at the FDA to further assess the robustness of the models we propose on the FDA funded clinical trials?

DR. LIONBERGER: I guess that's up to the industry to participate in sharing data that they have through the valuation. Certainly internally, when we use models, we test them against data that's available to us. We can't always share the details of those analyses, but we do generally try to share the conclusion. So if we tested a model against a whole bunch of different data sets, we'd say this model worked best.

So there are some restrictions on the data

there, but that's the approach that we generally take when we look at the models. But we encourage people to comment also on the use of modeling and simulation in areas where -- the question for the research activity might be what in vivo data would be most valuable for testing the models, testing the new bioequivalence approaches. So I encourage people to consider that as they prepare comments for the docket as well.

DR. ROBERTS: I have a quick comment. I I think the mucociliary process can be actually impaired in some of these disease states, and somehow that all has to be taken into account.

DR. LIONBERGER: All right. Any other comments in the inhalation area?

(No response.)

DR. LIONBERGER: So I want to change focus a little bit and talk about the topical dermatological area. One comment to trigger some discussion would be, as you heard from Lei's presentation, we've begun putting out guidances on approaches for Q1/Q2 formulations that are very

similar. But the question I'd like to hear research input on is if we want to expand nonclinical endpoint bioequivalence studies for topical products, the products that have potentially Q2 differences, what are the key research aspects in both characterization bioassays, in in vitro testing, in vivo testing, modeling and simulation that's relevant to understanding branded generic formulations that may have small differences either in their Q3 structure or the Q2 excipients in terms of the research that would be needed to establish bioequivalence tools that may allow us to approve products that have larger differences but would still be clinically substitutable.

DR. ROBERTS: You want me to start?

DR. LIONBERGER: Yes. Why don't you start?

DR. ROBERTS: So I have to say that one of the biggest problems for skin dermatological research is we're not measuring the site of action. We're actually measuring a fair bit away from it, and we need to get tools which measure much closer

to that site of action to know what's really going on. We have to also recognize that is not an easy task, and it has been for a lot of us for a long time. But the other part of that same ground is to recognize there are patients involved who have different responses, and the formulations and how we use them can also make a difference.

DR. ROSTAMI: I will actually follow on from Mike's comment, but going back to the example of inhalation, what happens if the opposite is true? So rather than actually having over discriminatory tests in healthy volunteers, we are having a test that is not distinguishing. But when we go to the patients, then the distinction becomes. Therefore, I would say actually understanding the physiology in the patients is much more important. I can't go further than that because, then I will be given actually away my talk this afternoon. But things that Gordon showed, they are wonderful. However, I will say that we have to repeat them in the patient population as well.

DR. LIONBERGER: Any particular aspect of

the dermatologic conditions that you think are most important for understanding, in the skin?

DR. ROSTAMI: From my perspective, is it the composition, how it changes. We are not talking about just a disease for which we are using the drug, but other comorbid conditions. The age effect, the ethnicity. I think the area actually Mike covered very well. But there are many variables that have nothing to do with the drug. I think we have to put more effort into actually understanding the system.

DR. ROBERTS: I think the other problem you have with dermatological is some of them don't work very well, so there's probably dermatitis and a range of others. We have a problem out there; we have some very bad products. But of course that's not part of your brief to make better ones necessarily.

DR. LIONBERGER: Our brief is to make equivalent products.

We heard some comments from some of the public comment period speakers on the potential use

of bioassays for Q1 -- potentialy non-Q2 formulations. Any comments on the approaches that were proposed?

DR. ROBERTS: I think the first thing is still the actual vasoconstrictor assay has been around for a long time. A lot of us now use non-invasive multiphotonimaging, and we're actually measuring the five responses directly in the viable epidermis. And we can actually measure change in redox state and range of others. I think there are lots of opportunities in that space, but it's very much a virgin territory.

DR. LIONBERGER: Scott?

DR. McNEIL: So I think a lot of it depends on how well the mechanism of action is understood and also the critical quality attributes because we're very good at generating data across the board, especially in the physicochemical realm, but does that truly tie in? I mean, it's the age-old argument, but if that mechanism of action is known, then you can prescribe a bioassay and back-validate that.

DR. UHL: As I heard some of the presentations related to bioassay some, some of it was emphasizing the animal data. Again, while the animal data could probably be used by a generic drug developer as they are trying to figure out formulation changes and its impact on equivalence or sameness, which are the criteria we have to evaluate, I question their usefulness as part of a submission to the FDA in a generic drug application because of the limitations of what can be submitted in a generic drug application.

So while they may very well be useful to industry when they develop, those data would probably not be part of a regulatory submission for an ANDA. They could very well be for a different type of submission, which would be a B2, but I think what we're really looking for here are what are the things valuable to demonstrating the sameness or equivalent so that a generic drug application could be submitted.

I don't know if there's thoughts, especially amongst the companies that are sitting around the

table related to that. But I think the usefulness for regulatory decision-making with animal data in the context of a generic application would be very limited from a regulatory standpoint.

DR. LIONBERGER: But I would say there's I think a role for the animal data in the research. So we have some collaboration with David Strauss and the group in DARS to do animal studies to help understand the mechanisms of these things, so you get some of these mechanistic questions. Particularly in the ophthalmic area, we've been doing something to help -- where it's very difficult to do any kind of human studies, that a lot of the knowledge comes from some of the animal studies as well.

DR. SEO: I have one thing to add to what Cook just said. We have the same experiences on the new drug side. Animal data, I mean it's useful when you're developing the model, but it hasn't necessarily translated well on when we're trying to make a regulatory decision. It helps tell the story about how you started the model and how you

progress with that, but at the end of the day, so far, you're almost better off using publicly available human data to do that kind of assessment, at least from a regulatory perspective. But there is a place for animal data. It's just it's challenging.

DR. SCHWENDEMAN: Can I ask a clarification on the scope of these comments? Are we talking about all generic type products or just talking about the skin before?

DR. LIONBERGER: Here we're talking specifically about something, but I think other locally-acting products.

DR. SCHWENDEMAN: Locally-acting products.

DR. LIONBERGER: But I think the question on the usefulness of animal data, if you want to address that, that certainly can cover some of the other -- move on to complex injectables later and talk about that.

DR. ROBERTS: The other question that follows on from the animal stuff is actually the microbiological stuff on the scheme. So there's

been a lot of work done on the human microbiome. Part of the other interaction is how does the skin interact with its environment and how does it respond. So you can use mass spec and a range of others to look at changes that occur, and some of that will reflect what your product's doing. And I think there's also issues of inter-day variation as well as inter-subject variation that we really haven't resolved yet.

DR. ROSTAMI: One comment on the animal side. Obviously, we heard from Dr. Naageshwaran with regard to the ophthalmic in use of rabbit eye. I heard they have measured transporters, but I am not sure how those transporters, for instance, actually match to what we have got in human. So it is not just doing animal or not doing animal, but if you're doing animal, we have to look at the translatability in the mechanistic vein as well, not just on the basis of a correlation because correlation is only for one or two compounds. You never know what will happen with the third and fourth and fifth. So that's very important that

actually translatability of the information and the physiology between those animal models are also established.

DR. ROBERTS: If I can just add to that, there's almost no information available out there on skin transporters in the viable epidermis and what they mean in terms of activity and drug action. That's sort of one of the areas with we know lots about expression, but not so much about a function.

DR. LIONBERGER: I'd like just to close out our discussion on the topical area and any comments from our industry representatives on the value of focusing work on expanding the bioequivalence approaches away from things that are strictly Q1/Q2. How much of a barrier is that to generic entry into competition if you say, well, if there's a requirement to match exactly the formulation components, how much does that affect or delay your development of potential generic products, if you're able to comment on that.

DR. SUN: Okay. I want to make some

comments. Actually from an industry perspective, once we move on to develop generic drugs, we understand we have to do the Q3. But Q3, we understand a lot of critical attributes. But the thing is how about the quantitatively related? Because everyone knows, yes, this CMA, we call it, have an impact, but how exactly is the impact, especially for some particular drugs?

So I know the FDA has a lot of databases, especially RLD information. So if they can provide more clearly what kind of critical attributes are most critical for this particular drug, and especially if not for guidance, for publications to demonstrate how the quantitatively relationship, what exactly methods can be used to do the research to identify these quantitative relationships. That will be very helpful for the generic industry to save money to folks -- more important the research in this area.

DR. LIONBERGER: Your requested is for a more precise definition of the Q3 characteristics and the methods for measuring them.

DR. SUN: Yes, exactly. Yes, thank you.

DR. LIONBERGER: So I agree with that, but the question I'm getting at here is to say how much is there a barrier if FDA puts out a product-specific guidance that says if the products are Q1/Q2, do this, how much of a constraint on generic drug development is that? How often do you say, no, I want to make, for whatever business reasons, a formulation that's not Q1/Q2 for some of the, say, topical or ophthalmic -- say topical products where Q1 and Q2 differences are allowed by our regulations?

(No response.)

DR. LIONBERGER: We'd appreciate the generic industry to consider comments for the docket.

MS. NAAGESHWARAN: I just wanted to quickly comment about the comments on specific reference to the ophthalmics. I think there are three things to be kept in mind. One is I don't think there's any doubt that the animal data really will not be part of the regulatory process, but it is very important from the perspective of the generic product

development because that's basically matching or mimicking the pathway taken by the RLD.

Secondly, to the point about human data, there isn't any. There isn't any human ocular bioavailability data. You go through any of the package inserts for any of ophthalmic products that were approved, and it will be very difficult to find anything more than aqueous humor at best.

Thirdly, about translatability, you have to keep in mind that this is a generic product, so you're trying to compare this to an RLD. So, comparative assessment is the only burden here. You have to prove sameness, non translatability. Within the innovator space, we do a lot of work with brand products. We characterize. We look at translatability of a preclinical model to human, but I think within the scope of the generic products, the only burden is to prove sameness to the RLD. Thank you.

DR. ROSTAMI: Can I take it? The translatability that we are talking about is actually translatability of the data you are

producing with the generic for the rabbit eye versus what will happen in humans? If the transporters are different and it happens that the formulation affects certain transporter, but the other one doesn't, how are you going to translate that into human?

So, that was the question. We do have the possibility of actually matching the transporter abundance in a human eye versus rabbit. That was my question, saying that has been done and we have got human eye bank that actually can do. These are part of the gaps that we are supposed to be identifying.

MS. NAAGESHWARAN: No, that's absolutely right. I'm not directly refuting that point. I'm just saying that when we're using this data, especially utilizing a model like IVPT, the only purpose is along the lines of how you would use a release test except that now you've actually got a relevant barrier like the cornea. But the rabbit to human is less critical in this case because all you're doing is comparing the performance of the

test formulation to the reference. The reference is also being evaluated within the same model.

DR. ROBERTS: Can I ask you a question? So, my observation, going to many conferences on imaging, is that people do multifocal imaging of the eye all the time. And one of the compounds you can image very easily is fluorescein. So why not in fact use fluorescein as a marker to look at what happens with various products? It's also transported, so you can actually use some of the available things to do in vivo studies, state of the art, noninvasive imaging. Why is that not being done more?

MS. NAAGESHWARAN: Oh, it is. We most certainly use -- there are fluorophoto meters where you can look at residents' time. You can look at tear turnover. This is most certainly an option as well, which is to use some of the imaging parameters.

DR. ROBERTS: We're talking about human eyes, both normal and diseased.

MS. NAAGESHWARAN: I'm not familiar with the

clinical space, but within the preclinical utilization of labels like fluorescein is certainly a way to compare, and provide a comparative assessment. But yes, it can be done in a human setting.

DR. ROBERTS: I'm just really trying to say that is an opportunity for you guys.

DR. LIONBERGER: Thanks very much.

So, let's move on to our next topic. We've heard a presentation from the industry on the importance of the complex injectables, formulations. As you saw also from Stephanie's presentation, there's a wide range of research activities in the liposomal nanomaterial, iron colloid, protein injectable, that all fall in the space of complex injectables, so a pretty broad category. I'd like to move the discussion toward the characterization and equivalence methods for complex injectables and open the floor for discussion in that area, specifically asking the industry, are there any particular analytical gaps that research could close that would lead to better

characterization of these materials in support of approaches toward equivalence?

Scott.

DR. McNEIL: A good approach to this is coming back to what was said earlier of are there other regulatory pathways like 505(B)(2). The reason I mention this is how close is close enough as was said earlier. So, a research area that we could discuss is defining those CQAs, because there is quite a bit of arm wrestling that happens between the reference and what is prescribed as a weighted attribute, if you will, because a follow-on can come in and they can match the physicochemical characterization. They can match stoichiometry size and so forth. But the true germane question is, is that specific parameter critical as far as biocompatibility, and safety issue, and efficacy issue?

So, research into what those CQAs are, not just because the reference product defined them in their original application, but because now with a body of knowledge, we can say, yes, this is

important and this is kind of nice, but it's not weighted as much as a certain parameter.

DR. LIONBERGER: So the comment there is really figure out which -- like I think it was mentioned in some of the talks from the generic industry, you can measure a lot of things, but you want to measure the most critical things.

DR. McNEIL: If you know what that critical thing is.

DR. ROSTAMI: I think, as you know better than me, at least in the EMA guidance, they are putting lots of emphasis in global sensitivity analysis, which is in the line of what you are saying, to pick up the most sensitive parameters. The fallacy of that is that in the majority of these complex models, we have got several of these parameters that are interconnected and correlated, and current systems of global sensitivity analysis to identify such dominant parameter is actually ignoring the fact that we can't have parameter A going up and down without actually parameter B at the same time going the opposite or the same

direction. So, we have to be careful, they have pushed for that but I believe, in the next guidance they are actually retracting that.

DR. ROBERTS: Can I ask a question, Rob? One of the questions, injectables, when I've written reviews on this, is what about the irritancy in injection? Is that well described? And what about the interaction with blood and exactly the disposition of those? How well is that characterized? I just don't know. Maybe someone could answer it. It's not my area, but nevertheless it's probably trying to open up the question.

DR. LIONBERGER: Generally, generic injectable, required by our regulations to be Q1 and Q2, so generally you're not introducing new irritants. The differences between the brand and the generic could be in the particle size, the distribution of materials. And those would be the questions that we'd want to either show sameness by characterization or have appropriate measures of equivalence to say I measured this difference, and

this difference doesn't matter because of our understanding, and we funded research in a range of these.

DR. ROBERTS: But do you actually have in vitro/in vivo correlations -- not correlations but some sort of relationships for the irritation?

DR. LIONBERGER: Not that I'm aware of.

Zhigand, did you want to comment?

DR. SUN: Yes. I just wanted to comment on something about that. Basically, especially for these long acting injectables, especially related to nanomaterial and the microsphere, I see right now the big challenge for everyone is there's no standard method available. A lot of research papers or publications are available, however how reliable is this data for these particularly small particles?

That's a question there because so many papers available, however how reliable is the data and how method is trustful, and which method is most sensitive? They have a lot of questions in mind that actually cannot be solved at this moment.

Therefore, from the generic industry, it can use a lot of methods to do a study, but which method is most sensitive to this drug, or how is later method validation, how reliable, especially when you do use some method -- for example, you're testing the RLD, and you found a big variability in there, so how do you interpret the data? It's because this method is too sensitive or actually this critical attributes is not that critical.

So, there are a lot of issues in there. So basically recently, we also work for the USP, and we highly recommended that we have some standard available like this typical method used for characterizing a nano material or microsphere. If we have that standard available, then we can more share the data. We use the same method, a validated method, so we compare all this data, and make more meaningful results or conclusions for all these products.

DR. LIONBERGER: Could you be more specific about which methods you're talking -- I mean, are you talking about particle sizing or material

characterization or drug release? Like which of those methods? If you think about the PLGA microspheres, like what?

DR. SUN: Yeah. They have a lot -- just like -- okay. For example, particle size, I've seen a lot of people already talk about particle size. For nanomaterials, actually, we also like something -- we have to use different method to measure. But how sensitive -- how comparable are these methods is still questionable.

For example, use SEM method or, use dynamic light scattering. But actually, everyone uses that, but how do you compare the data or how to set a spec, that's really very critical right now, and nobody seems they can answer this question. We asked USP right now, even though monograph is available for this high technical method. I think that's an area where there should be more focus from especially the FDA or from organizations like USP.

DR. LIONBERGER: Katherine, do you want to talk a little about --

DR. TYNER: No. I appreciate the comment about the need for having standardized methods for a lot of these characterization tools. I also appreciate that USP sometimes isn't as rapid as maybe we would all like it to be for that. So, I was also wondering if people wanted to comment on the fact of using other international standards, organizations, such as ASTM or ISO, which do develop some of these documentary standards to look at methodology because then at that point, you have a standard document that everyone can start off in the same place. Even if you have to vary it for fit for purpose, you have that initial document.

DR. SCHWENDEMAN: I guess I'd like to comment, if you're talking about something like particle size, I think that the answer is more straightforward. If you're talking about the release performance of one of these complex injectable microsphere products, this is where we run into a couple of really key difficulties. And the difficulty, number one, is that we don't understand why the release is different in vivo

than it is in vitro. We just don't understand why. So, that's number one.

Number two is even though you have some extremely well characterized products on the market, we don't fully understand the interrelated mechanisms by which those drugs are released. So, we develop an assay, an in vitro assay, and we've shown that actually a microsphere formulation can have a different key mechanism of release in vivo than a standardized in vitro type of tests.

So, these I would say -- and each microsphere product may have a different sweet spot. You may have a microsphere product that has a high loading that may be subject to dose dumping. You may have another microsphere product in which the drug can form a solid solution in the polymer. You may have another microsphere product in which the drug has a fundamental instability that can give rise to differences in bioavailability.

So, I think in my view, we need to do some key mechanistic research to try to better understand these things because if we don't, we're

going to be just making standards for the sake of making standards that may or may not be informative.

DR. STEIN: In terms of some of the discussion related to we can measure a lot of things, what are the right things to measure, from an industry perspective, it seems maybe there are times where a characterization that's highly relevant for one product, one route of delivery -- so for nasal sprays, a spray pattern clearly seems like a highly relevant method. It seems that some of those sometimes get translated to other routes of deliveries when you see the product-specific guidances, such as orally inhaled drug products where industry might have a different perspective on how relevant those are. And maybe just trying to understand the relevance of some of those types for different routes of delivery would be helpful.

DR. MANTOURLIAS: I would also agree for some complex projects; we need to understand the product by product specifically. So,

standardization is the best approach because, for example, it's really true that for different products, you have different loadings, different interactions between the API and the matrix. In some cases, it's the matrix that gives a release profile. In some, it's the API that governs the release profile. So definitely, I totally agree, that we need to be open and we need to study case by case and see what is really the release mechanism of these. That's why we need a lot of scientific understanding of exactly what is the [indiscernible] or the trigger that gives a release, that govern the release mechanism. And sometimes, for example, for some products, we give too much burden or too much focus on stuff, like PSD, particle size distribution. But we can see at the end of the point that we can be even broader with particle size distribution as soon as you fulfill other criteria for the release.

DR. SCHWENDEMAN: I have a couple of other questions. One is -- and we have been making microsphere formulations under FDA projects for

quite some time, and we are in the process of making the so-called Q1/Q2 formulations. I always have the question how do you know whether you have a real Q2 formulation? Particularly, there's a certain distribution, statistical distribution, of loading from the reference listed product, or you have distribution -- and then there's a certain uncertainty of your analytical method.

Has the FDA considered more detailed guidance to come up with a statistically rigorous analysis of what qualifies as Q2?

DR. LIONBERGER: I think that's a good comment. Some of the other challenges in that are, as you know, for the microspheres, the excipients that have to be, quote, "the same," are polymers with distributions of molecular weights and chemical structures. That's been a focus of some of the research activity in the past as well to begin to understand what aspects of those fit into the regulatory paradigm of same inactive ingredients for the injectable products. So, I think that's certainly an area of current

investigation and challenge in the development of these products.

We'll have comments from the generic industry on that in terms of specifically I think maybe turning toward the long-acting injectables that use more complex excipients. What has the industry identified as key challenges in understanding the properties and similarity of those excipients?

DR. MANTOURLIAS: I just wanted to mention also, for example, since we were discussing about these injectables, sometimes of course they are using the diluent, which is a vehicle. In most of the cases, also there are some excipients like [indiscernible]. It's a natural and curing polymer. Here sometimes it's very difficult. We have to decide, want to be Q2, the same qualitative or the same quantitative because then from excipient to excipient, this can differ a lot. But if we say that, for example, the outcomes would be that we need to have the same viscosity, for example, in this case, this is more important, more

relevant, then we say we are also trying to find the same three, exactly the same sequence, that gives the same composition.

DR. LIONBERGER: Thanks for that comment. Any other comments on the complex injections? What's up?

DR. ROBERTS: Steve, I tried that on petrolatum and had differences. It's the same issue of Q1's also can apply a new area. It must be. So, the source of your actual materials could have an impact.

DR. SCHWENDEMAN: Yes. And I saw some research focused on you get the polymer from a different source, and the manufacturing is slightly different. The blockiness of the lactic and glycolic acids and so forth, these potentially could affect the performance of the product. There are other aspects of impurities, the degree of residual lactide, or if it's like polycondensation, how much water-soluble acids are in the polymer. There are a number of different facets that are going to potentially affect the outcome. Sure.

DR. HOCHHAUS: I just had a question concerning those injectables. Do you guys know about batch-to-batch variability from the reference-listed drug product? Because that's a big problem for inhalation products.

DR. SCHWENDEMAN: Yes. That kind of gets back to the question about what's Q2 because if you have a slightly moving target of your reference-listed drug, it's not one value, the drug loading, for example, or how much drug is in the sample. It's listed on the product. It's supposed to be 8.5 percent for the Lupron depot, but, A, depending on how you measure it, it actually falls within that category if you measure it by an extraction. If you measure it by amino acid analysis, actually we get a little bit outside that. That drug product has a little bit too much leuprolide in it.

Then we do see some variation when we get different lots and so on. So how do you pick up that in some statistical analysis to give guidance to -- because some people may be too strict with

their approach to satisfy Q2. I mean, you have to be reasonable.

DR. LIONBERGER: Please identify your affiliate.

MR. TANTILLO: Nicholas Tanillo, Sandoz, Inc. One of the challenges I think generic companies sometimes face with drugs that are not required to be Q2 -- so we look at the whole universe of locally-acting drugs where you have the option of being Q1/Q2 or alternatively conducting a study of some sort, and is sometimes I think -- well, I think when a drug company submits a proposed formulation, say, in a controlled correspondence, they may be looking at a deformulated brand where they've done reverse engineering on the brand and based the formulation on that, and generate data on their own product post-formulation, submit that to the agency, and I think that the go-to document is the NDA, which has the, I guess -- I don't know who, the speaker this morning mentioned the material inputs.

So, the potential is there could be changes

or losses. So, when you're looking at what was then reverse engineered against what was in an NDA formulation page, they may not match. And I think in terms of patient access, there's a potential issue in that you submit a control correspondence under GDUFA, where you base it on data, and you get a response that you're not Q2, and then two more times, and you've got a year gone already. So, that's a challenge I think for some of us in the industry.

DR. UHL: This is Cook. So, Nick, do you have a scientific recommendation to the agency on this? Because part of that is really more legal, regulatory.

MR. TANTILLO: I hesitated bringing it up, but I just wonder if there's an opportunity to look at some of these locally-acting drugs. It takes a lot of thought in terms of the material inputs versus what the actual formulation -- what the actual patient gets. You know, is there an opportunity to look at some excipients that typically are used, even on locally-acting think

drugs like the immediate-release solids for Crohn's disease and that sort of thing. That's the closest I can get to a recommendation, Cook.

DR. LIONBERGER: But I think the recommendation might be -- we've published some work on the best characterization method to measure that. As we recognize some ideas for these things, it's a challenge to measure it accurately in the formulated product. And that's something that is I think in scope for research activities, both in some of our grants and contracts, and also some of the work that our FDA labs do as well, to say what's the best and appropriate method to measure and what's in the formulated delivered product.

DR. CRENTSIL: I believe I've heard a little about generic drug research in pediatric populations, so I'd like to complete a picture by pulling in the geriatric populations. I think as drug products get more complex and excipients get more complex, the higher the opportunity for age related changes to impact equivalence. And as you all know, as we age, we become more diverse or more

heterogeneous because of a variety of reasons. So, as we do research, if we could evaluate the impact of advanced aging of some of these things we've talked about, I think to be valuable. Thank you.

DR. LIONBERGER: I think we'll have more discussion on that in the afternoon session.

I'd like to move to a new topic. We heard a lot about quantitative methods and modeling and simulation in the different aspects of the research program, so I'd like to open up for some discussion about are there some overarching things that we should look at for how we use quantitative methods and mechanistic models in developing generic drug equivalence approaches?

Amin?

DR. ROSTAMI: I will say without preempting my talk this afternoon, I think that we are sometimes actually putting too much emphasis on the model. I have some statistics actually on what Dr. Zhang showed today. I analyzed the text of that particular presentation that I will talk about this afternoon.

The model itself doesn't do anything. The information that goes into the model does everything. So, we're modeling part of the equation, that whether it is compartmental; whether it is PBPK; whether it is micro sort of level; whether it is macro level; whether it is, I don't know, ordinary differential equation or partial differential.

These are I think secondary. What we have think about the model is actually what informs model. And most of the time that relates to the system, but also it relates to the in vitro kind of studies that we are doing. So, I think if you look at those and look at how discriminatory they are, how relevant they are, particularly with regard to patient population, that would be the benefit of everybody.

DR. LIONBERGER: Guenther?

DR. HOCHHAUS: I think those models are very, very important to learn how sensitive the system is with certain in vitro differences. So, it might be very, very important to come up with

acceptance criteria. For example, in the inhalation area, if you do computational fluid dynamic modeling, it essentially boils down to particle size distributions. So, those computational fluid dynamics are certainly very, very important to get a feeling for what effect does it have. But at the end, one maybe could use those modeling approaches to come up with certain acceptance criteria just for the particle size distributions, if those are the only input parameters for the model.

DR. ROSTAMI: But the key question here is that you are actually making that particular statement in a certain condition. What I'm talking about is actually to be able to extend that to all different conditions that they matter. So, you may say that, okay, particle size here is such and such, but I will do it another condition and say it doesn't matter. So, I think this is very important that actually we identify the relevant parameter space that we define these models and talk about them. And unfortunately, we don't do that. At the

moment, the best that we are doing is an average patient, or even worse, average healthy volunteer.

DR. HOCHHAUS: That's a question of what you should do in bioequivalence studies, whether the human being is a living cascade impactor or just use it to see whether the performance of a generic is similar to that of a reference product.

DR. ROSTAMI: That is the subject of my talk this afternoon because they interact.

DR. LIONBERGER: Okay. Any other comments on quantitative method?

MALE AUDIENCE MEMBER: [Indiscernible], the University of Florida. From a, a perspective of an academic, to start out, we always build very complex models to get the best perfect description of whatever we're after, and I totally agree on the input data, of course meta. I think there may be some space to kind of come up with a more decision-making regulatory type perspective to simplify these complex models and say what still captures most of what is relevant for a decision-making perspective and still is applicable

by a wide audience of users.

DR. LIONBERGER: In our remaining five minutes, I want to give the panelists an opportunity to comment on the sort of -- I picked four topics, but there's 15 different ones. So, this is an opportunity if there are any comments that you'd like to make on any of the things you've heard this morning that I didn't mention in these any specific topics or that are related to the presentations that you heard. So, this is the sort of open topic.

Scott, or Julie?

DR. KIMBELL: I wanted to just make a comment that when it comes to modeling nasal sprays, such as what we do, there is a great deal of importance placed on these particle size distributions. But typically the data that's collected is collected in a controlled environment where the spray is sprayed into the air, and then the particle size distribution is measured at 2 or 3 centimeters from the tip of the nozzle. However, that distance is hardly ever realistic in the nasal

passage, so it'd be good to have an initiative or some kind of push to get some information on what these sprays are like much closer to the tip, which is much more relevant for distribution of those types of sprays or even streams at that point in the nasal passages.

DR. McNEIL: So I found the first two presentations this morning very informative. I really liked the linkage, the connection between here's a problem, here's an RFP or a statement of work, and here's the research project, and even to show the metric of an ANDA. One thing that came up in I think both of those presentations, though, was the internal research versus external research.

So, I was just wondering how you're handling that as far as being able to put boundaries against those because there's a lot of competition in that area. Are you able to pick the right investigator with the right expertise? Are projects generated internally that have set-aside funds? I didn't want to get too much into the process, but I wanted to ask if you have the resources and authority

available to you to be able to select that best investigator.

DR. LIONBERGER: Right. From our perspective, we ask for input here into what we should do research on. Then once we've identified what research we are doing, then we'll look both at our internal capabilities, the labs that we have both here, on campus, and we have one also in St. Louis as well that have different internal capabilities and capacities, both expertise and their capacity to do the research that we've identified as priorities. And then we'll also then say which of these things maybe need to be done externally?

Essentially, all the human subject research, that's something that has to be done outside through contracting and grant mechanisms. The other work, quantitative methods, we can do a lot of that internally because we're not limited by lab space. Laboratory activities, measurements, we have a lot of capacity internally, but we don't have infinite capacity so that we have to look at

what expertise we have internally. Sometimes it's what expertise we want to develop internally and what expertise we can obtain externally because we want to collaborate with people who have capabilities or equipment that we don't have access to or capabilities here.

So, all of those factors go into whether things will be done internally or externally, but the resources that we have, we can use them either internally or externally, depending on what we think is the best approach to meet the objectives of our priorities.

DR. UHL: I appreciate your question. This is where we need input from the public on. That's why we have this public meeting, and we have a docket on what is important and also what is most important because we walk away from this meeting and the docket with probably a couple hundred million dollars' worth of research ideas. So, it's imperative to hear from external stakeholders, not just what research needs to be done, but kind of what is the most critical research that needs to be

done in order to advance the generic drug program here.

So, in GDUFA, for example, the Generic Drug User Fee Amendments, we are in year 6 of that, and over that five-year period -- I think you've probably had data on this earlier in the presentations -- the agency funded between 15 [million] to $20 million of research per year. If that answers your question about do, we have the resources available? It depends on what priorities you guys give us in order to try and accomplish that.

DR. LIONBERGER: Any other final questions on this topic from the panel?

DR. ROBERTS: Gordon Amidon spoke this morning about his enteric coated aspirin. We worked on this about now 30 years ago when we created one with GSK, and there haven't been any problems with it. My experience back at that time was not all enteric coatings react the same, and I'm just wondering to what extent there is an opportunity to look at what do the different

enteric coatings do in terms of that performance that Gordon was talking about.

DR. LIONBERGER: Celia?

DR. CRUZ: I'd just like to make a comment on the topic of what we should standardize versus what's critical because I think they can drive two very different approaches to research. Obviously, standardization of methods is something that we work a lot on. I think we've made great strides with PSD for ophthalmics, nanomaterials. Thinking of these issues is I'd say almost straightforward, and I think we can do it. And then it gets of high importance when it's determined to be for bioequivalence purposes and statistical methods and all that.

But I think the questions of what is critical is maybe the harder one. It might require more attention. If we go to the long-acting injections for example, there might be things that we are not thinking about. For example, what actually happens to this particle the moment it's injected and how the drug is released, I would ask

the research question, you have two products with very similar particle sizes but they're being injected differently because the viscosity is different or the injection site may be treated differently.

There are products with inherent variability in how they're applied and used, and sometimes that might be almost as critical as the particle size. So, there might be some blind spots that we might want to think about for these particular very complicated, not just how they're formulated but how they're used, products. So, I just wanted to bring that up that particle sizing, I think we can handle, and we demonstrated some good examples of that, and we can continue to work on that. But for these particular ones, there might be that next layer of complexity we should think about.

DR. LIONBERGER: Katherine?

DR. TYNER: And just to follow up on Celia's comment, I think this is something that was also brought up earlier. There's the question of what's easy to measure versus what's hard to measure. And

certainly, the things that are easy to measure we're going to measure, and we're going to standardize and make things about it. But the real crux and what we need to be focusing on is is what's important to measure.

DR. LIONBERGER: So I'd like to thank all our panelists for participating this morning. We'll have a lunch break. Before, I just have an announcement. We found one vehicle claim check left here, so if you use the FDA valet parking and you don't have your -- it will be up here.

We will reconvene at 1:15, so thank you all very much.

(Whereupon, at 12:19, a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:18 p.m.)

DR. LIONBERGER: Welcome back, everyone to our afternoon session. Again, the focus of the afternoon session will be on identifying new research priorities for generic drugs, so we'll begin the afternoon session with three talks. The first talk will be by Jeff Jiang, who's the deputy director of the Division of Therapeutic Performance in the Office of Research and Standards, and he will talk about newly approved NDAs that may pose challenges for generic drug development and may also be areas where research activities are needed.

So, welcome, Jeff, to provide this overview of changes to newly approved products.

Presentation - Xiaohui Jiang

DR. JIANG: Thank you, Rob for the nice

introduction.

So, welcome back to the afternoon session of the GDUFA Regulatory Science workshop. Here in the next 20 minutes, I'm going to talk about the potential research challenges as a research program moving forward by looking back at some recent approvals of the NDA product. So, once they approved, those will be the new reference-listed drug, and what are those and which kind of things we need to think about.

First, the time span we looked into the past three years. From 2015 to 2017, as you can see, each year under the NDA path, you have probably 100, or sometimes more approvals, for the overall NDA products. Those include the B1 and the B2. We're also looking further into those new molecular entities, so those are really the NMEs, and those are usually the B1 products. Each year, they are certainly up and down, so something around 30 approvals for those new entities.

In the GDUFA II, we do have a commitment, which is for those developed product-specific

guidance for those non-complex NMEs. Right now, is the starting of the GDUFA II, but we're also trying to do those things along the way. If we look back, the GDUFA commitment is by fiscal year, so that's why there's a slight different shift of the number because we're counting here by fiscal year. In 2015, we have 27 non-complex NMEs and all the guidance we have developed. And again, for FY16, we have 21 non-complex NMEs. For those, all the guidance is developed, so on and so forth. At '17, we are catching; it looks pretty good. And for '18, so far we have 12, and some of them already in the pipeline but just have not been published. So, the published ones include something like the products that will be eligible for a biowaiver and those things are counted as published.

So, moving forward, we're also looking to the complex part. Those are the criteria or what we consider a complex product in the GDUFA II, so it can encompass complex active ingredient, complex formulation, route of delivery, dosage forms, and the device combinations. So, each of them, it's

very narrow, but on the other hand, it's all those things coming together to define the complexity as well as the last one. So far it's abuse-deterrent formulations, although are oral, but we consider them complex as well.

Looking to that, considering that for each year, let's draw another graph. Here we already know how much each year if we're looking to the percentage. So, if we normalize it, each number is an absolute number of NDAs. So, for each year, we have about 25 or 30 complex drug products in that paradigm. And at the very top, those ones we call transitional products under the BPCI Act, so the protein will become biologic. So, those are insulin products. Let's just be clear on that. So, insulin products, we are not planning to do any further research into that because those will be regulated as biologics after 2020.

So, for those complex products, if we look, we didn't promise anything for the complex. We will do our best. We conduct research to provide guidance as soon as possible, looking at what's the

performance on that for the complex products. So, that's what we did. For FY15, we have 20 complex products approved during the year, and we developed about half of that. And in the 2016 fiscal year, we have about 30 such products, and we are about a third.

So, as you can see, we do activity in those areas trying to develop those guidances as soon as possible as permitted, or at the same time, if we see there's a gap, what we do is we conduct regulatory research. So, research certainly takes years. As soon as we can have a solid result, we can feed those into the guidance, and we will do it as soon as possible.

Let's dive into those complex products to see which -- if we look at the route of delivery, for example, the majority is the injection category, so including suspension, emulsion, or an API complex possibility as well. Then the other three -- the inhalation area is certainly still very big, dermatological stuff, and oral, surprisingly, you have 16 percent oral. Those are

primarily ADF formulation, abuse-deterrent formulation, as well as locally-acting formulations. So, we think those are complex, and we need to develop the guidance on how to address the bioequivalence. And they're a very small percentage of other things.

Another way we look at it is we see there are significant overlap between different types of categories. Showing here, those are three different categories. One is complex API from the lower right-hand side. We do have you looking at the overall number. In the three years, we have roughly about 17 such products, but some of them intersect with device as well as dosage form.

That's really an unique phenomena we identified. It's not simply put that into the complex API bin or the device bin. Especially as you can see the device, the formulation, and the complex dosage form, there are significant overlap. So, those are the things we work with different teams, internally work together as well as in the research paradigm to see how to address those

problems simultaneously.

Looking to some details, the challenge in the complex API area, we identified a number of things, some of them already ongoing. So definiteily in the past three years, the peptide product has approved a lot, so they have increased. For example, those with an aliphatic tail, last year we had approval of Semaglutide, which have a sustained like -- itself it's still a solution formulation, but you can do it once a week. So very, very good profile and for the diabetes indication, so how to address some of those challenges there.

In that particular area, certainly we have done a lot, as this morning's session already mentioned. So particularly, we still continue on the impurity part as well as the immunogenicity assessment using the nonclinical method. So, the overall guidance was published last year. For the polymeric drug compounds, that's still a growing area. We have made quite a success in the Sevelamer colesevelam part and also the first

generic approved recently, and we're still taking on other polymeric drugs.

The oligonucleotide is something coming more recently, and it's a new class of APIs we need to look into. So particularly, I'm showing two examples. That's the first one, this one approved in 2016 and it's a neurological indication.

Now, look at a structure; here is a structure. It's quite large, 30 units linked together. Another important part is in the enlarged section showing its backbone is modified, unlike peptides, which that's a signature. It keeps the same amino acid in my bond. That's sort of the amino acid backbone. The nucleotide they have to change the backbone to make it druggable. In that situation, how do we do those analytics? That's something to keep in mind. That's another one approved in the past three years, and this again is for a neurological indication. And this one in the so-called area also changed the backbone as well as the sugar part. As you can see, those are very subtle changes with a quite significant

challenge when we talk about API sameness as well as -- that's the challenge. So how do we establish API sameness to get the identity right? So, that's a challenge, as well as impurity. Those are usually made through a peptide-like synthesis. Add one another one, each on to each other. Assuming in the peptide paradigm, I gave the example, if they assume the success rate, the yield, it's 99 percent. So, after 10 units, you've got about 90 percent. After 20 units, you drop to 80. Below 80, then 70. So, there are lots of other impurities in it. How do you control it? Because for the new drug, they went through the clinical study, so they know what it has. And for the generic, those are injections, and for the bioequivalence part, it's eligible for biowaiver and how do we do that, ensure the safety profile? That becomes a very important part.

That's one of the areas we're going to look into and develop the capability, either internally or outside, through a relevant to mechanism. And another of the things that we're looking into is,

as I said, the device involvement in those either with API or with the complex dosage form.

We further looked into that intersection. As you can see, just looking into the intersection part, the inhalation, nasal, really stands out as a challenge, as well as the injections still have those auto injectors as you can imagine. The other is device related, so have an implant or other kind of stuff put in the human body.

The one stand out on the top is smart drug and what do I mean by smart drug. In the next couple of slides, I'm going to show you some of the unique drug products approved recently, and this is the so-called smart drug. It doesn't mean those things that have issues, have problems, or to develop a generic drug version. Here it's just to identify some of those challenges for the research where we will look into and figure out how, and put those findings into a guidance as soon as possible.

This one, the so-called smart pill, this is really the first oral product, which has a tracking function. There is a small antenna. It's called

ingestible event marker embedded with the oral pill. Also, they're going to provide you a small patch to put on your body. But once the pill gets into the GI tract and triggers a signal being sent out, the receiver receives it, record it, and also with modern age, everybody has a phone, have apps running there, so your phone, your app, will receive that signal, log the event, and so on and so forth. So, a lot of things, as you can imagine, being shared with your physician as well as other people you choose to share.

It's a whole new paradigmm, a new system. So, with that thing in place, how can we test the equivalent generic for the ingestible event marker system, for example. That's a challenge. So, we need to figure out all those things. So, that's really new age stuff.

The next one, this one itself is not that different. Exenatide has been marketed for quite a long time, even for the extended release, the PLGA formulation of exenatide has been on the market as well. But that's a relatively large peptide, 30

plus amino acid less than 40. The unique part for this one, this is a device which the patient can use for the injection. In the past, most of those extended-release injectable was administered by the house professional. So, you'd have to go to the doctor's office. A nurse probably gave you an injection for those extended release. This one is really in a pen, which is used by a patient. So, what kind of features, which kind of safeguards need to be in place for this to be successfully used by a patient.

This is an implant. This is for nasal implant. That's a very interesting looking device, but you release the drug from that device. So, the device itself has certain requirements for its material, for its safety. On the other hand, on top of that, also the drug-release profile needs to be considered, as well as when we talk about device, how do you put it in, which kind of things, procedure, and so on and so forth. So, when develop a generic thing as you can see, there's a lot of stuff that needs to be matched so that its

safety and efficacy profile can be ensured.

Transitioning to the inhalation nasal part, there is sumatriptan for the migraine. In the past, probably as you all know, those are delivereed by an injection, emergency injection. So, you took it out and trigger it. This one is really unique. The API is the same, but using a nasal delivery part. And by doing that, you're using your mouth as well to help that delivery. So, that's a very, very interesting part. So, for this kind of new device, how do we do the equivalence? Although the API part should be a straightforward. For the same concept, instead of delivering the powder, this one delivers the liquid spray form. So, through the nasal with your mouth to trigger to help it. And that's a device component.

This kind of complicated stuff we already have quite a program in those areas, the nasal inhalation area. This will be the new, office get into it. The last example here, probably this is not brand new. You've already seen that in the

past, but really it is something we're still working on, the Soft Mist. This is an inhalation product. Really, how do you characterize Soft Mist? It's a dynamic process as well as the impact on the inhalation. We already talked about quite a lot of inhalation this morning, so this just adds another layer of complexity to that.

So, that's pretty much what I want to talk about and show you this afternoon, just really as an eye-opening saying we have been working on a lot of things and achieved a lot in the past five years and started a new GDUFA II and looking at some of those recent approvals in the past three years. There are still a lot of new challenges and a different device, API, and a different area. So, we still keep on working and identify those things along its way, and really plant a seed because certain times down the road, the generic company will start to develop those drugs. So, we need to have the science, the technology, and the guidance ready to face those challenges to help work with the industry to really move forward in those areas.

Thank you for your attention.

(Applause.)

DR. LIONBERGER: Thank you, Jeff.

Our next speaker is Amin Rostami from the University of Manchester and Certara.

Presentation - Amin Rostami

DR. ROSTAMI: Thank you very much, Rob.

I have put this together to bring up, as I was given the mission to highlight some of the gaps that I see that are happening. You can see from the title that it's actually given the line that I'm going to go through. When I was preparing this, it was interesting for me, that is almost quarter of a century since I started to look into the bioequivalence, and to be honest, my view hasn't changed.

I see still bioequivalence as a clinical measure because the debate on whether it is quality, which Rob brought up earlier this morning, versus clinical. Still to me, it's more clinical. We want to have a product that, as the aims of this workshop was saying, they are substitutable, but at

the same time, they have got efficacy and safety measures that we would like to see.

Going forward of how I see bioequivalence, they are in this -- and most of the things that I'm showing, they are already published, apart from this and anoother piece. This is under review, and hopefully it will come out soon in J Pharm Sci. One of the things we have tried in this piece together with my esteemed colleagues actually to indicate is that understanding the system parameters -- being a systems pharmacology professor, it's very important for me that it is important for bioequivalence, too. And this is what I'm trying actually to put to the GDUFA and the fees that they are coming from that should be spent.

So even though I have focused on the modeling side a lot, today my message is that when we started many of the things that are related to bioequivalence, when you look very early on and it has continued with the same line, one thing that is missing in all of these assessments is all the

time, patients. I know that this is a little bit -- I would say no contentious issue to talk about the fact that we are doing all the time in healthy volunteers for one reason or another, but the questions that we have to ask is, is the bioequivalence going to be actually different in the patient population than healthy volunteers? The answer is it might be, and I will show you some of those cases.

But then, do we have to do our bioequivalence studies in patient population? The answer is not necessarily. So how we actually decide on this, that's on the back of doing what we call virtual bioequivalence studies. So, these studies are actually to help to understand, in which case we have to do these studies and in which cases we don't have to. But then when we can rely on these, and that depends on the performance verification of these models, and these verification of the models is not -- as I mentioned this morning, it's not just about the equations that we are putting in place, but the information

that we are supplying for these models. And this is something that, unfortunately, sometimes it actually is not appreciated much. People are focusing too much on the models and much less on the information that supplies the models.

I did, as I said, the statistic quickly on the presentation by Dr. Zhang this morning, and it was amazing for me to find that in that particular Powerpoint, there was 50 times mention of "model" but when it came to the patient, it was only four, and all those four were under patient perception. Then I said maybe I have used the wrong actually word, and I put "disease." And there was only twice that disease was mentioned.

So how this actually becomes important, it goes back to the starting point for me, when I started to look into IVIV and PBPK, what I call new PBPK because the old PBPK didn't have this IVIV. And it was on the back of this one sentence in this particular publication by the Swiss Regulatory Authority that quite rightly they were saying that the cause of many of the problems, they are not

actually the average people, but they are theoretically conceivable extremes of the population, which you can't actually test. Even for the NDA, as you know, the blue area that you are showing is our focus, so we never actually tested drugs in the overall population, and therefore the information are lacking and we cannot actually look at all those different elements that they are composing the population.

But the other thing is that many of the guidance that we have got to look into these, the guidance's that they are saying to into these intrinsic factors extrinsic factors, but it is hardly actually looking into a combination of these. But really, patients are actually having a combination of these, and therefore even when we are looking into one parameter, another parameter, and defining into the real world, the situation might be very different.

So, the models these days, the PBPK models, they are actually built of many, I would say, submodels, and that's the reason they come under

the systems biology systems pharmacology, and each of these little models within there, whether they are PK related or PD related, they need to be informed by lots of information but only once for that particular, let's say, organ, but under different conditions. And from that moment onwards, you can start to look at those different variations that we talked about in the virtual space.

Why this is important? Because when you look at the combination, the number of study arms, you assume that you are having a formulation effect, but the formulation is together with another drug, and, no, you are having some effect on transporters, et cetera. You want to figure that out. The number of the arms that you will have to consider for a study becomes impossible. Some people have tried with only two or three elements, but it becomes quickly impossible to actually study all of them.

Whether these are actually relevant or not, we are starting to appreciate, yes, they might be.

So, if you look into, for instance, bioequivalence in healthy volunteers, you may come up with no difference, and this is the formulation effect, not the API effect, but because of the differences in the stomach dissolution that's happening as a formulation, now if you move to HIV patients who are receiving, let's say, antiacids, then they will have a completely different profile.

The same applies with regard to ethnicity. Seventy percent of over 70 years old in Japan, they have got achlorhydria. So, if you are actually doing something in the healthy volunteer, 30 years old, 40 years old, whether that actually is relevant to that group or not, that's another angle. Whether we should do all the time these studies, my answer is no, but we have to actually assess these and see when we need them or when we don't.

The same applies with regard to drug-drug interactions. If you are having two drugs that they are sufficiently similar but they are slightly different, how do we know that their drug

interaction susceptibility is the same because we are only looking at their efficacy and safety on their own as a substitution, but we are not looking at their DDI. That could happen.

This is something that we are preparing at the moment, and we have actually looked at the formulation effect, and we know in the case of ketoconazole and midazolam and how it actually impacts the level of DDI.

The most interesting one for me, this comes actually in the American Journal of Kidney Disease. As you can imagine, I am not a regular reader of this one, but this was because they were referring to one of our work, so I noticed that. And that comes when you have got in Caucasian, when you are switching from one formulation to another formulation, there was no difference with regard to the clinical outcome, et cetera. But the same switch in black African Americans caused lots of side effects.

This was in my view predictable because it is all happening because of the location of the

CYP3A in the GI tract and the fact that Afro Americans have got lots of these, a group of them. They have got much higher actually representation of it, abundance of it.

Therefore, the difference between these formulation, they were exaggerated in this group. And for those people who are interested, particularly the editorial in this one is very, very nice written and very simple without going too much deep into science with just references, but it is highlighting how these things can happen.

But the question is if you want to define all of these into models and rely on models, whether they are giving us answer or not, we rely on actually defining the system, and defining the system requires doing samples in these patients for the system parameters. And LCMS proteomics is one of the ways that we are looking into it.

I hope that GDUFA starts looking into some of these. We were very disappointed that when he invited actually speakers from FDA for the ISSX meeting, they said this is off their area. To me,

this is exactly the kind of thing that we should be doing. Thank you very much.

(Applause.)

DR. LIONBERGER: Our third speaker is Howard Chazin. He's the director of the clinical safety and surveillance staff in the Office of Generic Drugs.

Presentation - Howard Chazin

DR. CHAZIN: Thank you. Today I'm going to give you a little primer on our approval process, what the clinical safety surveillance staff does with generic drugs, some of the focus on how the postmarketing safety resources that we use are addressed in some ongoing research and the questions that are raised, and limitations to these resources. We're going to talk a little bit about the clinical significance of observed differences between brand and generic. I'm going to give you an example, all in 10 minutes.

Often when we give these talks, we throw this pyramid up to remind everyone that the foundation for generic drugs is built on layers of

information that we rely on before we go up the line. So, we understand a lot about the chemistry, and that builds a foundation for pharmaceutical equivalence, which then once that foundation is solid, we build the next level of bioequivalence. And then very much so during the approval process, we consider clinical relevance, which is also therapeutic equivalence. But we think about the clinical relevance of the formulation in the target population.

As was alluded to before, we had different requirements because ANDAs are abbreviated, new drug applications, we don't expect everything in an ANDA because the API has already been thoroughly tested. What we do, if you do notice on this list, the chemistry manufacturing controls, generally the labeling and the general testing of the chemistry and pharmaceutical equivalence is the same. The difference is that formal animal and clinical studies are not done for ANDAs because this was done during the NDA phase 1, 2, 3 process. So, we really rely a lot, again as you know, on

bioequivalence to support the ANDA approval.

Because of that, we expect generic drugs to be safe, but the difference is that, in formulations, we also don't always know when generic drugs go into wider populations, if there are going to be issues. So, the clinical safety surveillance staff addresses the formulation differences in generic drugs by surveying and being a liaison to CDER's Office of Surveillance and Epidemiology. The OSE office handles the active pharmaceutical ingredient related safety issues specifically, where our group tries to focus in on what makes the generic different. And in those differences, are there underlying safety issues to particular generic drugs.

So, we have two teams. We have a data team and a clinical team, and only the small group of us are focusing on the issues coming from all directions across the organization. Plus, we help as an umbrella organization across the rest of the Office of Generic Drugs to address premarket safety. The things that come in during

bioequivalence studies, we review those bioequivalence serious adverse event reports and also postmarketing when products get on the market, and then we hear about maybe issues that are going on specific to generic drugs, and our group takes the lead on those issues and helps also to support the science research, the postmarketing and premarketing safety research.

One of the resources we use is the FDA Adverse Events Reporting System, and research is going on to see if others could use the public FDA databases to address issues of surveillance, but FDA itself, the adverse event reporting system is limited. It's difficult to identify, for example, brand versus generic in FAERS. Many times, -- and there's a lot of research on this -- reports that come into FAERS from the public, especially and from other resources, misattribute the generic to brand. So therefore, some of the data analysis isn't always supported because you can't identify specifically either brand versus generic or the exact generic.

Sources in some of the reports can be unreliable and they can be duplicated as well. And public FAERS, there's no way to de-duplicate the reports to try to get rid of multiples. They're often incomplete, and they don't include the narratives. And that particular safety issue in a FAERS report may not be specific to the generic formulation that we're concerned about. Again, a lot of the issues are focusing on the active pharmaceutical ingredient.

So in essence, to try to use FAERS, a postmarketing safety system that's very large and has these limitations, makes it difficult to identify and verify. And other reasons too are that in patients, once the drugs do get into patients, there are concurrent medications and illnesses that keep us from understanding whether or not there's an exact relationship between the adverse event and the single drug that we're focusing on.

Another good resource that we've used lately is -- it's been renamed. It was IMS. But IQVIA is

a source of drug utilization data. And what this database does is it collects drug distribution across the country. And as we know, drugs change in distribution of market share over time, when generics come online, their uptake can be rapid or it could be slow, depending. But what happens is that the RLD, the reference-listed drug, usually slowly decreases market share over time, and then the generics predominate. But that happens over a time period, so we can look retrospectively to see when those events are occurring and if a particular drug that has a high market share, a particular generic, is having a specific issue.

For example, there are many generics of methylphenidate, and we have a lot of complaints about some of them that come in that are direct acting, short acting. So, we have to decide if we get -- our group, we do a monthly assessment in our internal databases, and if we get, let's say, 10 complaints per month for 3 months for a drug that has 10 percent of the market versus 10 complaints for 3 months for a drug that has 50 percent of the

market, when are we going to pull the trigger, do a further analysis? So, we must use those and these internal databases to help us.

FDA also has the Sentinel Initiative, which gets a lot of press, and it's also being used in research to see if we can then use a cohort analysis to see if we can detect safety issues in generic drugs. But it's limited to retrospective data and requires some specificity. However, there's been some success in looking at data on switching between generics and brands, and it kind of gives us some underlying clues as to why a patient might switch from a brand to a generic or from one generic to another if they perceive that it's not working right. Perhaps we could pair our sentinel data with this IQVIA drug distribution data to help us identify specific generic drugs related to how market factors change.

Now sometimes patients perceive a generic inferiority, so we allow differences in generic drugs. Sometimes generic drugs can differ in shapes, scoring, release mechanisms, et cetera.

And here's an example of Prozac where the RLD is orange and blue, yet four generics look very different. So, when the patient picks up their medication and gets a new refill and the generic looks very different, they can feel that they got the wrong medication, or that it doesn't work as well, so we already know there are perceptions based on just how a pill or capsule may look.

We get a lot of different kinds of quality issues and complaints as well that we try to consider when we are doing our postmarketing assessments. You can read the slides yourselves. But on this little picture here, we once received a complaint about tablet size. And you may not be able to perceive it very well from this picture, but the three tablets to the right, below the other two, are a little thicker than the rest of them. And we got this complaint from the Office of Compliance because in the manufacture of these tablets, there was a filling issue where the tablets filled a little too much, and the overfill created these thicker capsules. And we were asked

was there a patient related health risk issue. And we said, yes, there could be because these may not split correctly, people may think, again, that they have the wrong medication, or they may not crush the same way, so they were removed from the market.

Now I want to give an example of something that happened only a few months ago where our Office of Surveillance and Epidemiology received a complaint about generic olanzapine. Olanzapine is an antipsychotic medication, and it has an orally disintegrating tablet formulation, that way you can just dissolve the tablet. We have a guidance for this that says it's a solid oral dosage form that should be dissolved in 30 seconds or less.

So, the NDA, Eli Lily’s formulation is a lypholized, freeze-dried blister tablet and disintegrates almost immediately. Most of the approved ANDAs are soft compression tablet that disintegrates between 15 and 30 seconds. This is not -- this is an illustration of in vitro dissolution differences, and we've talked about the in-vitro bit. But here you see that they don't all

dissolve at the same rate or time. Not all of these on this picture are FDA formulations. But allowable differences in these ODT products, disintegration up to 30 seconds makes physicians, nursing staff, and healthcare providers believe that it's not dissolving, and therefore working. Therefore, the generic is perceived as inferior, but yet the generic product met all the criteria for approval.

So, research on perceptions when patients switch from RLDs to generics is valuable. And it's challenging because its subtle perceptions aren't easy to quantify in research. So, we've looked at some of these other drugs in this way directly by looking at patient substitution studies. So, as we talk about this later on in our discussion, think about other drugs that are prone to patient concerns related to substitution, and hopefully that can lead us in our research. Thank you.

(Applause.)

DR. LIONBERGER: Thank you, Howard.

So, what we'll do now is we're going to take

a short break, and we're going to begin again at 2:10 with the open public comment period. So please be back here precisely at 2:10 so we can begin on schedule. Thank you very much.

(Whereupon, at 1:58 p.m, a recess was taken.)

Public Comment Period

DR. LIONBERGER: All right. So, welcome back to the open public comment period of this workshop. We'll have again five speakers. The first speaker is Ilene Harris, so welcome Ilene.

DR. HARRIS: Thank you for selecting our topic for presentation at the public comment period. This is a great slot to have because it's the first. It's right after lunch. Everybody's rested and fed. First, I'd like to acknowledge my colleagues, Zippora Kiptanui, Paula Dowell, and Jingjing Qian, and you'll be hearing from Jingjing next.

But before I get started, I wanted to just tell you a little bit about some background about our team. IMPAQ is a public policy evaluation and

research consulting firm. I lead the pharmaceutical health services research practice area. Our largest client is Health and Human Services, and we currently have several cooperative agreements and contracts with the Food and Drug Administration. The proposal I'm presenting today is a product of some of that work that we have accomplished in collaboration with our academic partner, Auburn University. I'll review the background and rationale for the research priorities, as well as the proposed methods.

Our motivation for this topic comes from background work we completed on our FDA projects, as well as our subject matter expertise in drugs and drug policy. As you're probably aware, of many drugs that are prescribed for use in children are not labeled for use in children, and some of the statistics are listed here on the slide. In fact, off-label use in children is generally accepted as standard medical practice, yet, there is evidence of increased risks of adverse drug events in this population that may or may not be known to

prescribers and patients. To further complicate the issue of off-label use in children with regard to generic drugs, generics may be used off label for indications that are carved out relative to the reference-listed drug and again with potential for knowledge gaps among prescribers.

Generic rosuvastatin is an example. In contrast to the reference-listed drug, Crestor, it lacks any pediatric labeling, and any use of generic rosuvastatin in pediatric populations would be an off-label use. Addressing our proposed research priorities will provide insight into pediatric use of this and other generics with carved out indications as well.

So therefore, we propose the following research priorities. First, to determine which generic drugs, clinical specialties, and adverse drug events are most prevalent with off-label drug use in children, and second, determine the information sources used by healthcare providers as clinical guidance when generic drugs are off label in pediatric populations. We believe that

addressing these priorities will provide insight into off-label generic drug use in children, thus improving the FDA's ability to assess postmarketing use and safety of generic drugs in pediatric populations.

For the first priority, to determine which generic drugs, clinical specialties, and adverse events are the most prevalent with off-label use in children, we propose a mixed methods design. First, it would be important to complete a literature review and comprehensive environmental scan to identify the drugs that are most frequently used off label in children. Then we will confirm that the drugs identified in the scan are indeed off label by reviewing the FDA labels.

Then we propose a quantitative analysis of administrative claims, similar to the IQVIA data that Dr. Chazin mentioned, to estimate off-label drug use in children as well as an analysis of FDA's adverse event reporting system, or FAERS database, to describe the reporting rate of adverse drug events for off-label use in this population.

And as you heard previously from Dr. Chazin, this database has many limitations and challenges to do this type of work, and we recognize that. Responding to this research priority will provide insights into generic off-label pediatric drug utilization patterns and adverse drug events.

So, addressing priority research, question number 2 would determine the information sources used by providers when prescribing off-label drugs in children. For this question, we propose conducting an environmental scan and key informant interviews to determine how clinicians obtain this information. For example, we will examine which drug manipulation, such as crushing solid dosage forms, or opening capsules, or diluting drug solutions, which of these are frequently used and with which drugs to facilitate administration of drugs to children, particularly when the existing dosage form of a drug is not available or not suitable. We'll explore these issues across a variety of settings, including outpatient, inpatient, and emergency departments.

Based on some preliminary interviews we've conducted with pediatricians on generic drug use, we found that this approach provides insights about existing clinical resources for off-label pediatric prescribing and identifies priority areas for resource development and future research directions. Our findings can inform the development, for example, of a nationally representative survey of prescribers on these issues.

The IMPAQ team is uniquely qualified to address these research priorities because of our expertise and experience in the methods proposed: environmental scans, literature reviews, drug label reviews, analyses of administrative claims, and adverse event database, as we've have accomplishments in all of these areas as well as key informant interviews and surveys.

We have two current and one completed cooperative agreement with the FDA on the topic of generic drugs, and our team, IMPAQ and Auburn, has worked successfully with the FDA on projects to

better understand and address various aspects of generic drug utilization.

In summary, the proposed research priorities function as postmarket evaluations by determining the prevalence, characteristics, and frequency of adverse drug events with off-label generic drug use in children, as well as identifying the sources of clinical guidance used by prescribers when using drugs off label in children. Results of the proposed studies will provide insight into off-label pediatric drug use patterns, thereby improving the FDA's ability to assess postmarketing use and safety in pediatric populations.

For example, the proposed studies will identify sources of clinical guidance used by prescribers. This information can be used to identify priority areas for the FDA to encourage clinical studies to improve pediatric labeling of these drugs, especially if there's evidence of adverse drug events observed with off-label drug use. As another example, the proposed studies are designed to examine the frequency of adverse drug

events when a generic drug is used off label for a carved-out indication. This information can be used to guide the direction of additional studies needed to determine the safety of generic drugs when used off label for carved out indications. Thank you.

(Applause.)

DR. LIONBERGER: Our next speaker is Jingjing Qian.

DR. QIAN: Hello, everybody. Thanks for the opportunity to speak at the generic drug workshop today. Today we are going to talk about another potential research priority that FDA might consider, to enhance comprehension of generic drug information among patients and caregivers, especially those with low health literacy. I acknowledge my colleagues at IMAQ International, LLC.

We are going to talk about the background first, then we propose research priorities, and also a recommended methodology to address those research questions. We all know that generic drugs

play an important role in controlling healthcare costs. It is only 10-20 percent of the price of the brand drug, however, the savings in the past 10 years for the U.S. healthcare system is very significant.

One of our research projects collaborated with FDA. We looked at the potential key stakeholders of generic drug use. That includes patients, caregivers, as well as providers such as physicians, nurse practitioners, pharmacists, as well as formulary managers and policy makers, and also of course the manufacturers, as well as the retailers such as the drug chains. Their relationship with each other as well as their individual impact on generic drug use is significant.

Previously, earlier this afternoon, we talked about the, patients' and caregivers' perceptions regarding generic drugs, if they have negative feelings or perceptions about generic drugs, which might impact the use of generic drugs, and even the efficacy and safety of patients when

they use generic drugs. Regarding this, FDA developed a variety of educational materials targeting patient education regarding generic drugs.

Another ongoing project that we are working on with FDA and IMPAQ, we are recruiting patients doing in-person surveys and interviews to ask their opinions and perceptions based on FDA developed patient educational materials regarding generic drugs to look at their input and their feedback. This is an ongoing survey and based on preliminary data of 70 patients. And half of them -- after they review FDA developed materials or handouts regarding the generic drug approval process, as well as a cost and safety efficacy information, more than half of them told us that, hey, this really improved my perception and my understanding about generic drugs. However, a considerable portion of these patients also reported that the material might be long, complicated, and too much text. Their feedback, at least a few quotes here, not enough pictures, or please use more simplified

terms and reduce the medical terms.

This information really gave us the feedback that -- although the federal and the state agencies develop those materials, it's very important to make sure that patients, especially those with low health literacy, they have access to the material and they can understand the material. That's why the educational effort to promote generic products should account for patients and caregiver’s health literacy and cultural backgrounds.

Regarding this topic, we propose the following research priorities. First to identify the best practices and resources for generic drug communication directed at patients and caregivers with low health literacy, and then to examine FDA's generic drug educational materials for appropriateness for our patients and caregivers with low health literacy.

To address the first research priority, we propose first we can look at systematic review of literature and clinical guidelines or toolkits to look at how the materials are available for

provider and patient communication, especially if they address the health literacy issue. Then we can interview the policy makers as well as healthcare providers regarding where they find the materials or resources to help them to improve the communication with patients with low health literacy.

Because of the collaboration between IMPAQ International and us, Auburn University, we are at a school of pharmacy, and we have ongoing long-term continuing education for pharmacists and technicians in Alabama and also other neighbor states -- how to disseminate the information that we received based on this research priority, to disseminate what are the tools or materials available to enhance the healthcare provider and their communication with those patients.

To address the second research priority, we propose that we can use different methodologies to evaluate FDA developed educational material regarding generic drugs. First we can use validated tools to identify the patients and

caregivers with low health literacy both in urban and rural settings. Then we give them an interview as well as focus groups to receive feedback on patients' perceptions of those materials, whether it's effective and how to improve the material.

As Dr. Harris just previously introduced, we has ongoing research projects with FDA. Especially, one is targeting generic drug substitution in special populations such as older adults and pediatric populations. And the second one is educating groups, influencing generic drug use. Specifically, we develop educational materials regarding generic drugs and disseminate those materials among different type of stakeholders, for example, patients; for example, healthcare providers and policymakers, and to gain feedback from those key stakeholders so that the information we receive, the evidence we got, can help us further revise the educational materials that we develop, and as well can help FDA to further improve the educational material and future development of new material.

Regarding the expertise per se in this area, such as pharmaceutical health services research, quantitative/qualitative research experience and background, this team of IMPAQ and Auburn, we already published a bunch of studies using this method that we proposed, including both qualitative and quantitative studies. Thank you.

(Applause.)

DR. LIONBERGER: Thank you.

Our next speaker is Stephan Schmidt from the University of Florida.

DR. SCHMIDT: Good afternoon, everybody. As a disclaimer, the views represented in this talk do not only represent my view but those of the team at the University of Florida. And I would like to acknowledge my collaborator Josh Brown from the epidemiology group, and hopefully our collaborators at FDA also think that this makes some sense.

So just a little background on a modern system-based approach related to efficacy and safety questions following generic substitution, to put this in perspective, 88 percent of the

prescriptions filled in the U.s. are typically generic. It has been reported that between 2005 and 2014, this has resulted in a cost saving of about $1.7 trillion, but also the U.S. FDA receives complaints, more or less frequently, about purported adverse events due to the lack of efficacy or safety following generic switching from brand to generic. Obviously, assessment of these complaints can be challenging, so we hope the strategy that we are proposing will be of help to FDA to evaluate these complaints.

The research strategy that we developed is that we want to develop a quantitative, integrative approach that will separate postmarketing signals from noise. And if this signal is deemed credible, to develop a strategy using quantitative methods and modeling to provide insights into causal mechanisms.

How does this look like? I put a picture up here for the workflow that we used in this analysis, and this is basically a three-pronged approach. The first step is basically that we use

an epidemiology approach to look into databases that we heard about earlier, including FAERS, but also a Medicare and Medicaid, or commercially available databases such as children to see if we can detect a statistically significant signal. And once the signal has been detected, then use physiologically based absorption modeling as well as PKPD models to drill down on the causality of the purported adverse events to see if that seems reasonable to occur following generic switching.

We applied this approach to a three case scenarios. The first case study was for antiepileptic drugs. We chose that drug class because if you look at, for example, the image RA [ph] guideline, you see that the biopharmaceutical classification system, as we heard earlier today, was used as one of the criteria in the risk categorization, so it contains drugs of PCS classes 1, 2 and 3.

The second case study was an extended-release scenario. We had used metoprolol. It's a complex, a modified release formulation.

And the third one was basically a proactive case study, that we decided to look at direct-acting anticoagulants. These are drugs that are currently still on patent, so to potentially provide FDA with some guidance if there's maybe one or more drugs that they should look at once these drugs come off patent. So for the sake of time, I would like to focus on one case example, and that is a metoprolol today.

With respect to signal detection, we know that formulation problems were reported within the first year of metoprolol extended-release use, where public knowledge was in about one year of launch. The hypothesis for detecting formulation issues would be that the generic uptake, also called market share, will be decreased as compared to a product that has no problems. Patients would discontinue treatment or switch back to trade formulations at a higher rate, and that the event rates for indicated conditions will be elevated for generic versus straight formulations.

We decided also -- and that was mentioned

earlier by Dr. Chazin I believe, that we should use an active comparitor, and we chose amlodipine versus benazepril for the reason that it was basically launched about the same time and has no known formulation issues. So what we see here, if we compare these two formulations and look at the market uptake, is that amlodipine is about at the market share that we would be expecting, so around 80 percent versus a metoprolol is somewhat lower, close to 73 percent.

We also see that if we compare these two formulations in a time-to- event analysis, basically, so time to discontinue treatment, that we see a slightly higher signal or a significant signal for metoprolol versus amlodipine. And then if you look into clinical event rates in terms of ER visits versus hospitalization, we also see that I'm metoprolol seems to be significantly higher than amlodipine.

So what we then did in a second a step is saying, okay, we believe that this is a credible signal, so let's now link what we know about the

formulation, dissolution testing, absorption, and how this translates into bioequivalence testing, into an overarching framework. We basically prospectively predicted the in vitro dissolution based on the composition of the formulation and then simulated out what this means in terms of PK. When we look at the in vitro dissolution profiles, based on the formulation, composition, and manufacturing conditions, we see here as the black line, that's basically model predicted line. For in vitro dissolution, we pulled out the respective data from the NDA and AND documents showing, okay, we can actually predict what was observed in dissolution testing, and then we varied the dissolution rate. So we basically increased the dissolution rate and then ask the question how much can we vary the dissolution rate until the in vitro dissolution profiles would be deemed an equivalent. And what we see here is that we have to have a fairly significant change, so 40 percent or higher, until these formulations become an equivalent.

Then of course the question is what does

this mean in terms of bioequivalence. If we then put this different in vitro dissolution profiles in as the pharmacokinetic input into the PBPK model, you basically see the same picture here, that if you look at the 20 percent change in dissolution rate as the test 1 here, then this would be still bioequivalent, but if you have a 40 percent or more change, then we would actually have a bioinequivalence in both Cmax and AUC for two different dose strengths.

Then we asked the question -- obviously, what we're interested in is the therapeutic equivalence. And when you look in the literature, what you see here is that exercise-induced heart rate is frequently reported as a pharmacodynamic endpoint. And we used here as the baseline the target, excercise-induced heart rate for 30 year old, and then 50 to 80 percent of maximum according to the CDC guideline, and we see that under those conditions, none of this changes, and dissolution absorption would result in differences in therapeutic equivalence.

Having said that, however, we need to recognize that the exercise-induced heart rate is not necessarily a sensitive enough metric to distinguish between any differences in formulation aspects. It's basically like a guideline by the CDC on how you should exercise, not more, not less. So we decided to go one step more physiologic and look at the underlying physiology and recognize that metoprolol is deemed a selective beta-1 [ph] receptor antagonist. We also need to recognize, of course, that we have both sympathetic as well as parasympathetic at play here and potentially also a loss of selectivity at higher concentrations.

Therefore, we had a quite frequent exchange with our clinical team, and it seems that they had significant signals in terms of brand versus generic use in heart rate variability, also also reported in the previous study from 2006, and that is what we are basically working on to see to what extent changes in PK would result in changes in exercise-induced heart rate.

If I had to summarize a case report from the

FAERS database that a male complained about chest pain, I would say, conceptually this is possible, but certainly more work is needed on a more mechanistic basis to evaluate the signal.

So in terms of of work that needs to be conducted, I I recognize certainly and appreciate the comment that Amin has made earlier. I think system components are critically important to understand, so what does that means in terms of healthy subjects versus patients? For example, if you go into an afib patient, what does this mean in that scenario here?

I also would like to acknowledge the comment that was made earlier, and that was the quality of the excipient because, obviously, you can use the established framework to simulate out various conditions as we have done. And for the sake of time, I have not shown these results. For example, if you modify the content of, for example, HPMC, according to the conditions outlined in the SUPRA guidelines -- where you have like a 5, 10, or 15 percent change, that is on a massbasis. It does

not allow you, however, to distinguish based on the quality of the excipients, so you don't know, for example, if the [indiscernible] and the porosity of that is the same, so I would encourage also some further research to be done in that area. Thank you.

(Applause.)

DR. LIONBERGER: Thank you very much.

So our next speaker is Stephen Byrn from Purdue University.

DR. BYRN: Thank you. I'd like to make a presentation on the on behalf of NIPTE, covering our certificate program in quality by design and quality culture. This program is a four-course certificate program, and the courses are offered in what we call blended format, which is a combination of online and face to face, hands-on presentation. The program is created using modern educational strategies such as backwards design and the logic model, and the courses are based on existing courses in the NIPTE schools, which are rigorous, which have already been established as rigorous,

high quality graduate level courses.

The certificate would be endorsed by the NIPTE board of directors, which would be 17 deans of schools of pharmacy, chemical engineering, and one medical school. So they'd have some academic, significance to them. And in some cases and at some schools, the courses can be used for credit towards master's degrees.

We have some ongoing courses, so I thought I'd hit the high points of a couple of the student responses. The students responded -- in this particular case, this student indicated the courses changed their thinking. The practical sessions were amazing. We're happy to receive these kinds of comments. "They shifted my mindset," they're saying, and they allowed them to think more about risks and analyzing risks. Another student talk about building community and the importance of observation and working in groups and decision-making and teamwork activities, and tapping other people's skills to solve complex problems.

We use a game we called the supply chain game. It's based on the old MIT beer game on supply chain, but we do with pharmaceuticals. This is extremely popular and could be done pretty quickly. You can see these students had nice comments about that. It helped me have a holistic view of the supply chain. It's a fun way to demonstrate amplification. Here's a person talking about their aha moment, realizing that everybody has to work together. This game, you're not allowed to communicate the different units. We have an API supplier, a manufacturer, a distributor, but in the game you can't communicate. So it's pretty interesting to see the results and those students really get a lot out of it.

So overall, the certificate program is aimed at a series of outcomes or key competencies. The first one is we don't want to miss the key scientific comprehension, the deep comprehension required to do quality by design and quality control and quality culture. We also include continuous manufacturing as part of this segment.

We are very interested in presenting regulations, and in fact, I'm on a recruiting mission here. That's the main goal of my presentation. We're trying to recruit FDA faculty to work with us. So as you'll see as we talk about implementation, maybe we'll put a sign-up sheet, but actually I'm sure we'll do it by email. But we are planning, as you will see, to carry out the course and the location where FDA can participate.

We want to cover quality. We'll cover communications like the feedback showed just by just by carrying out the course. One of the factors that we want to emphasize is strategy, regulatory strategy, culture, and quality strategy. Then we can't forget to ethics, so that will be a key element. And critical thinking obviously is something that we want to impart to all those students, and then the ability to integrate the program.

We're talking about four courses at the launch. The first one would be a background course in industrial and physical pharmacy with some solid

state chemistry thrown in. And we've had existing courses at several locations, so that course would be a combination of those existing courses. The second course would be a pharmaceutical manufacturing course including a hands-on laboratory. That would be at either Maryland, Long Island, or Purdue, or some combination of those locations. Each of those schools have very successful pharmaceutical manufacturing lab courses, and it's amazing to make product and you can learn a lot about quality when you do that.

The third one would be a biopharmaceutics course, and that course would be a combination of Michigan and Maryland and perhaps other schools, Purdue, so that course is ongoing. And then the fourth one would be a capstone course that Ajaz Hussain would organize that would include quality by design and quality culture.

Those would be the four courses that are roughly equivalent to 3 hours credit each, and there would be special emphasis in those courses on process understanding, pharmaceutical development

and formulation, and especially with hard to formulate and narrow therapeutic index drugs. And then finally, fundamentals of pharmaceutical manufacturing and continuous manufacturing.

So the implementation would involve a mixture of online and live courses. The online part would be run on on a computer server route of NIPTE. The first course would be at a hotel near White Oak. We've already been communicating with various hotels. The instructors would include NIPTE faculty, and this is my proposal that we would have FDA faculty. So actually we haven't certified or solidified that step, but hopefully the FDA people that are here interested enough in this concept that maybe they would come over to a nearby location and give a couple lectures. The live session would be here in a local hotel, and we'll do case studies, group work, and a few lectures.

Then to conclude, some of the other subject areas that we could go into and address, both in the certificate program and also in a master's

program are listed here, including issues related to global leadership and ethics, medical devices and diagnostics, and advanced manufacturing. I just put as a second concluding slide our diagram that we use at Purdue of our global regulatory science professional community. We found that it's extremely successful to link our graduates from our programs at Purdue, both certificate and masters, from the U.S. to our existing African program in Tanzania, and to build a global community of regulatory science and biotechnology professionals. So that would be the long-range goal, to build a global community. And I think I'll stop at this point. Thanks very much.

(Applause.)

DR. LIONBERGER: Thank you.

Our final speaker is Eugene Choi representing Medicines for All.

DR. CHOI: Good afternoon. My name is Eugene Choi, and I'm the executive director for the Medicines for All Institute at Virginia Commonwealth University in Richmond. We are

working with the Bill and Melinda Gates Foundation to develop low-cost manufacturing processes for global health drugs, including for HIV, malaria, TB, and other neglected tropical diseases. And today I'd like to take the opportunity to highlight some anticipated regulatory challenges envisioned by our model to improve access to critical medicines and the potential emerging and enabling capabilities and technologies that will enable widespread delivery of critical medicines worldwide.

But first I'd like to introduce who we are and what we do. Our motivation stems from the fact that lack of access to critical medicines, global health medicines is still a global health challenge. We have made some progress. Last year was the first time ever that over 50 percent of people worldwide were diagnosed with HIV and actually received ARV treatments, but it's not enough. The bottom line here is that 4 million people worldwide die every year from HIV, malaria, TB, and other neglected diseases, so we know we can

do better.

Our mission is driven by a unique approach to provide low-cost manufacturing processes to manufacturers, which increases the number of suppliers in the marketplace. We're also reinventing how we mitigate the vulnerabilities in the medicine supply chain, which includes starting processes all the way back from commodity chemical feedstocks, which are immune to market conditions and market volatility. And to sustain the culture and approach toward driving down costs of medicines, we're educating and training the next generation of global scientists by combining academic ingenuity with industry practicality.

We're also collaborating with students and visiting scholars from all over the world, including from high burden regions who want to train with and take home the skills and knowledge back to their home institutions. By empowering the next generation of scientists with global perspectives, we believe that this is the best opportunity to sustain the drive toward cost

reduction of medicines.

So most if not everyone in this room understands the current API manufacturing landscape, where the primary cost drivers are usually the high cost of raw materials or starting materials, high solvent consumption and waste generation, and inefficient chemical and manufacturing processes. These vulnerabilities lead to a lack of access and to a fragile supply chain.

If we look closer at the cost components for drugs, if we look at innovator drugs, R&D costs are usually large. That means that the API costs are just a fraction of the drug costs for innovator drugs. However, if we look at generic drugs, R&D costs are much lower and API costs can typically drive the 40 to 70 percent selling price of generic drugs. What this means is that these high API costs for generic drugs becomes a barrier to increasing competition and prevents new and low-volume drugs to come onto the market.

So we're taking advantage of these

inefficiencies in the current API manufacturing landscape by developing low-cost manufacturing processes that enable API costs to be a minimal driver of generic drugs. We're also developing models and approaches that are applicable to both high volume and low volume drugs as well as drugs both in market and in development. We're also developing novel manufacturing platforms to enable scalable processes, and we're developing greener chemistries that use less toxic materials and generate less waste.

This is a schematic of our typical process optimization and implementation approach. We first start conduct optimization where we identify and address the primary cost drivers. They can range anywhere from high starting material costs to very low yielding reaction steps or overall processes. Once we develop a low-cost process, we then either directly engage with manufacturers or work with our tech transition partners, including the Clinton Health Access Initiative and USAID and others to help manufacturers adapt their processes and help

track the market price reduction in global marketplace.

This is an example of our very first HIV drug, nevirapine, where we developed a low-cost process, was able to transition it over to multiple generic manufacturers, and then realize a 10 percent reduction in the market price, and that's the cost of the API. This is a portfolio of targets that we're working on for the Gates Foundation as well as for others. This is a portfolio of drugs that we've either already pursued or are in the midst of developing a low cost process for and have future plans on pursuing.

In addition to open sourcing our process to manufacturers, we're also developing our own manufacturing platforms as well as working with partners who have already developed their own platforms. This will help enable a distributed manufacturing paradigm. And we are currently working with country governments already who are interested in developing a local manufacturing and supply capability to deliver critical medicines.

This ability to deliver a message anywhere in the world is very empowering, especially for those developing countries that can now control their own destiny by delivering medicines to their own citizens. However, with these emerging trends and advantages come some anticipated regulatory challenges.

So as the barrier to entry into pharma markets is lowered, we're starting to see an emergence of smaller and non-traditional players come into the pharma markets. As you can see in the bottom graphs here, we've actually observed a significant growth in pharma activities in the global health community in a very short period of time, and we expect this to continue with the democratization of pharma manufacturing, both with the chemistry, but also with the flexible and distributed manufacturing paradigms.

So with that increase in pharma activity and in global health collaborations, we expect to see an increase in tampered, contaminated, and counterfeit products into the global health

community. So we have to address the QA/QC of both products and processes. In regards to addressing a QA/QC for both products and processes, there's already ongoing activity in developing PAT capabilities that are integrating to control systems and feedback for every unit operation for a given process. For example, one of our partners, MarqMetrix based in Seattle is already working with the FDA on developing online analytical measurement technologies that can verify quality attributes at every single point along the supply chain, starting from raw materials all the way to formulated drug product.

We can't forget about the back end of the supply chain, and some potential solutions and some outside-of-the-box thinking might lead you to developing or leveraging blockchain technology in order to attract every data source in the supply chain, tracing it back to the raw material supplier, all the way to when the medicine is in the hands of the consumer. By leveraging and implementing cloud-based sensor and data collection

technologies, this combination could provide a secure tracking of medicines in the logistical and distribution cycle of the medicine supply chain.

So I'd like to just briefly thank all of our collaborators and partners both on the technical side but also in the global health community. In summary, I hope that I've provided some food for thought for everyone in this room. We have made some progress in terms of improving access, especially in the global health community, but we have a lot more work to do, as well as trying to think about and address some of these key regulatory challenges that are sure to come up. Thank you.

(Applause.)

Panel Discussion

DR. LIONBERGER: Thank you very much.

We're now going to begin our panel discussion for the afternoon session. As a reminder to the panelists, you can address questions to the speakers in the afternoon session as well as your comments to the record. Again, our

goal is to identify what should be new research priorities that have come out of these discussions related to generic drugs.

I think we'll begin with just breaking it up as we did for the earlier session into topical areas. So we heard in this session about different populations and the idea that products will be used in a wide variety of patient populations, and what's the best way to ensure substitutability in those different patients and populations. So I'll open it for discussion on that topic. We heard also about differences in pediatric populations. I think generic use in different patient populations I think would also fit into this subtopic discussion area.

DR. ROBERTS: I can start off with a case study in the sense that one of the studies we're looking at are patients who are admitted to our hospitals were on between 10 and 20 drugs due drug adverse reaction. Many of those were actually generics, and the question is how do we know whether it's a generic issue or whether it's a

proprietary drug issue?

I'm going to put the question to Amin. Do we know from studies on bioequivalence whether there's an issue for these patients?

DR. ROSTAMI: I will answer it this wa. Lack of evidence is not evidence for lack of effect. It could be, but the problem is that we can't go and study all of them or expect from the regulatory perspective that all the generic companies should be doing all these different studies. Unless we have a mechanistic and good reasoning that this might be the case, I will say no.

So if you have got any reasoning -- I brought up that Afro American population, but in those cases, we knew that the discrepancy between the beginning of the intestine versus the lower power, that group is going to be bigger. So whatever that we have come up with the formulation that is equivalent in the Caucasian, it is likely that is not going to be equivalent because in that group, that discrepancy is much bigger.

So unless we have got a reason, I will say, as Stephanie showed, there is no reason to believe that it is because of generic. Many of them, they are just perceptions. With the modeling and the right sort of data, we can simulate and say that this is unlikely.

DR. ROBERTS: Even with hypochlorhydria?

DR. ROSTAMI: Hypochlorhydria, that's a different matter. But again, you can test it and see it had indications of PPR or the the Japanese that I showed. If the formulation or the drug has got -- rather for what reason the combination with the formulation causes a different dissolution in the acidic media versus the [indiscernible], you have got a warning sign there.

DR. ROBERTS: So I just want to add what you see in this population is people with dry mouth. You see them with usually stomach acid, which is is low, with this high pH. You see a whole heap of this lack of tears in their eyes. There's a whole heap of issues that they have at the same time because most of these are [indiscernible].

DR. LIONBERGER: I think with the question on, maybe Mehul can comment from OCD's perspective on drug-drug interactions. Is there any place that you see formulation related drug interactions instead of API related drug interactions, as companies develop labeling for their brand products?

DR. MEHTA: Good question. As Stephan was -- I like his work, and to be able to pick up signals like that, I think that will be the way to go. These are some enhanced properties of the drug substances in terms of interactions. The scale may shift a little with formulations. And again, I think only with certain formulations. As the comment was made, for us to get that done even at the new drug stage, it's not an easy task. So we need to design most informative studies and a lot of other information, otherwise it will be difficult to even approve new drugs.

DR. ROBERTS: If I can just clarify, the issue is the confounder of 10 medicines or more that these patients have because of comorbidities.

The message for me from this meeting -- because I'm doing a study -- is if I need to work with a generic or not. That's sort of critical information that we never thought about before, but perhaps we need to capture.

DR. CHAZIN: I have a few comments. There are several things. Once we start to get better databases that identify the exact NDC codes of what patients are taking, I think that's going to help us. And also the market data helps us because we can pinpoint a time frame for when maybe there's a certain formulation on the market that's being used in certain populations.

If we could get at some of those questions through different angles and be more precise with some of the information, we can maybe start to answer some of those questions. I don't know if we'll get at the polypharmacy API issue because that's another trend that's occurring in this country. As medicines become cheaper and people go to specialists, we're seeing everybody get on more numbers of medications without someone

programically [ph] taking people off, or as people go in for symptomatology, they've got to take more and more medications.

So that may be a separate clinical issue, but I think if we start to get more at the aspect of identifying generics in the distribution space, we might be able to start to answer some of those questions on formulation and their direct effects.

DR. SCHMIDT: I have actually a question regarding new drugs. To what extent are you seeing let's say formulation related issues between development and to be marketed formulations?

DR. MEHTA: Sorry. Repeat the question. So are you seeing the interactions --

DR. SCHMIDT: I would suspect that obviously if you bring a new drug on the market, you're not having a full-fledged formulation program. So I would suspect that along the process where also the formulation is evolving, that there's also maybe like a potential signal between a development and then a to be marketed formulation. And obviously that has implementations on the translatability of

clinical trial results.

DR. MEHTA: Well, one of the assurances we make for sure, in the formulation history, the development of a new drug, is to ensure that whenever the efficacy data is coming from the pivotal trials, that formulation and that efficacy is to be translatable to what is to be marketed formulations. So that's what you call clinicals [indiscernible] to be marketed. That's established to bioequivalence.

It's not necessarily that all the drug interaction studies, all those studies are done on the to be marketed formulations. A lot of times the formulation doesn't change. If it changes during the development, those are really minor changes, but we don't expect the innovator to repeat the clinical pharmacology program for what is to be marketed. We just get the assurance or the [indiscernible] of the pivotal efficacy findings.

DR. ROSTAMI: Just a clarifying question, to my knowledge that in the DDI studies, the

interacting drug that is requested to be studied against your drug in the development, that is not defined to be specific formulation. So in the label, you will find that it is saying drug A and B have got this interacts, but it doesn't say with what formulation of drug B.

So that is the question, thatn when you are putting the generic of drug A, whether its interaction with drug B is still going to be the same or not. Particularly, there is a big component of the intestinal blockage, then you know there might be a slight shift of the window of absorption and might not have a big impact on the concentration time profile because you have shown the bioequivalence, but it might have a big impact on the drug interactions.

DR. BULITTA: Jurgen Bulitta, UF. While I wholeheartedly agree on the use of advanced computational methods to address both disease and formulation related factors, I would be even perhaps more interested in identifying either existing or future experimental models which allow

us to probe formulations, specifically aspects of pathophysiology and disease state. So I would love to see thoughts on what models do we have to mirror certain complex diseases and what does industry think should be developed in the future.

DR. LIONBERGER: To answer your point, the way I would frame that question for the panel is what is the specific situations, either in special populations, or disease conditions, or drug product characteristics that FDA should pay research attention to, to identify if there is the potential for a real problem. I don't know that anyone has brought forward the real problems, but in terms of being proactive in terms of the research foundation, what are some of the characteristics that you think would -- either patient characteristics or product characteristics that should be subjects of of research.

DR. ROSTAMI: I'm guessing that we have to look at the patient target group. As we said, they have got the least amount of information. So when we talk about geriatrics, I would say that they're

originally full of gaps. We don't know how the geriatrics, different elements of the physiology and biology really is different. We are just starting to get there. Pediatric is the same. So I think those elements are definitely -- from my perspective, they are important for us to get into and understand those.

DR. SCHWENDEMAN: I think I may have mentioned earlier there are certain cases where the susceptibility to inflammation at the injection site can potentially have a significant effect on on the performance of the product. So that would then fall into the category does generic product A produce more or less inflammation than the reference listed, or what fraction of the population would be more susceptible to having much higher inflammation than the rest.

Those are the types of questions that I think would be valuable. Then can we study those in animal models, the effect of inflammation on the performance of products. I think that answer I believe is yes.

DR. HOCHHAUS: One certainly can learn from the history of innovator. Before the generic comes onto the market, if one would study or have databases where problem cases were reported, then for the Office of Generics, one certainly could ask the question, okay, should we have some special tests for that specific drug in that specific patient population.

DR. LIONBERGER: The challenge that makes that difficult -- and I'd like input -- is oftentimes we do see differences in a healthy subject versus a patient population for the brand product. That's a common expected observance. The challenge is that we want to identify for generic drugs is the case where your determination of bioequivalence, your comparison of your test-to-reference product in population A and population B would lead to different answers.

So the set of things where population A and population B are different is much larger than the set of situations where A versus B is different -- the T to our comparison is different

in
A versus B. So I think that's where we want to focus our thinking about in terms of the research, where are either the product related or the patient related situations where not just that there'll be a difference between the groups, but there'll be a difference in your test-to-reference comparisons between the groups? I think that's what we'd really appreciate input into.

DR. UHL: It sounds to me as I'm hearing this that a lot of this sounds -- it was in an earlier slide -- possible. Right? So there's the potential for this. So before we spend a lot of time and effort and money on investigating something that potentially exists, do we need to use, for example, database systems that are available at a patient level who are taking these medications to see if there's any signal? And then once there's a signal, to then think more on a molecular mechanistic basis to try and tease this thing out.

Because it sounds -- like I said earlier

this morning, we have limited resources for this program. Do we want to -- we're not NIH with lots and lots of money. So on a priority level, figuring this out on a mechanistic basis, is that a high priority for us right now or is it a bigger priority for us to figure it out on a population basis, as are there any signals that actually show that certain patient populations actually have differences if there are formulation changes? Because right now what I hear is it's possible, it's a theory, but we don't even have any data to say that there truly is a signal there.

DR. ROBERTS: I just wrote up a review in terms of drug absorption in the aged [indiscernible], and I compared the aged to the young. There are some drugs you see changes in the absorption in the elderly, and some you don't. It seems witht those where you see the changes in the elderly, maybe they're the ones you should look at for that situation, for that particular population. And you could do that for all the other populations, what are the drugs that we know are

behaving differently in that population compared to the young group you normally do your bioequivalence for? You might look at that. You might decide the physiology doesn't matter too much, but it seems to me that would be a good risk averse way to sort of start off with.

DR. ROSTAMI: My take on your comment would be -- well, that's the reason I showed the Afro American versus Caucasian, obviously that they are different. You are fixing them on the basis of the trough level, and they are showing lots of side effects, which is showing that the Cmax is actually higher.

But my comment -- maybe I misconstrued what I wanted to know to accurately convey -- is the reason that we have got that signal, which is whichever way that happened, nw we know the signal, we have seen it, this should not constitute going and asking every company that has got something to go and do the study. And the only way that we can do that is to actually build a good system for that particular case where the mechanisms of that signal

are well known in GI tract, CYP3A4 differences, generic variation as well as data upon those in different regions. Once we've built that, then we have the comfort of saying that, okay, we can actually predict this, predict that, all the old signals, and we don't have to do every single case and go and ask this drug needs to be now studied in the Afro Americans for bioequivalence.

So that was the way that I was coming. So I was saying that even if the signal is there, we should not be constituting from that moment on that everybody should be doing these studies in that group.

DR. LIONBERGER: Sarah?

DR. DUTCHER: I'm going to take a step back and actually talk about trying to identify those signals because I know we've been successful at identifying some, but I think the science of trying to identify potential issues is also in need of some additional development. I know there was definitely work in GDUFA I that taught us more about FAERS and its limitations. We've used a lot

of signal identification, and work I think is going to increasingly be in secondary data sources like electronic health records and administrative claims data

So I think that there needs to be more work done around that. Typically outcomes have been more on the safety side, so for example, Sentinel is set up to look at safety, but here the outcome is really substitutability and therapeutic equivalence, so you have to look both at safety and efficacy or effectiveness outcomes. So I think there's additional work to be done there, and it ties into this topic of real-world evidence that we hear often about.

DR. LIONBERGER: Stephan?

DR. SCHMIDT: So when we look at a signal, let's say we find a credible signal, how ready are we to interpret this also outside the bioequivalence realm? For example, if we have like a change in PK let's say by -- I'm making this up -- 20 percent, and we find in the analysis that maybe compliance is a more clinically relevant

issue. So obviously if the patient is not taking a drug for one reason or the other, this 20 percent change in PK may or may not matter. So how would you take this then forward for a decision-making process?

DR. DUTCHER: That is a hard question. I think it depends on the drug, on the situation. I think you're right, that looking at compliance or adherence to a drug is a key piece of information that needs to be incorporated in these studies. That hasn't always been -- there is a little bit of work showing that some people who take generics actually have better compliance, better adherence because the drug is more accessible. Making that decision is the big challenge, and the more studies we do and more comfortable we get with this type of data -- and you have to complement it with other sources. No single data source can answer I think the question. I think you really have to -- to get evidence.

DR. SCHMIDT: Sure. And then going back to what Amin said regarding the patient population,

the majority of the patients are of older age, let's put it this way, and taking at least five drugs or more. So drug-drug interactions again in combination may have an equally big impact. So I'm not sure if you are saying a little difference in PK may or may not matter that much from a clinical point of view, but obviously you want it to ensure the quality of the product that you have.

The other aspect I wanted to touch on is that I wholeheartedly also agree with Amin that studying each and every scenario or clinically is neither cost nor time effective. So I think the combination -- and I agree with Jurgen on computational and experimental tools is certainly worthwhile, and FDA has done I think a very good job there, that actually looking at the possible center [indiscernible] of metprolol in the clinical study in patients to see formulation differences in fact would make an impact. At the same time, it will help narrow down the options that we're looking at and saying should we be treating PCS class 1 compounds different than BCS class 2

extended release different than immediate release products, Caucasians different than African Americans.

So I think a combination of the tools is very helpful, and I think FDA has done a great job supporting these efforts.

MR. TANTILLO: I just wanted to add, perhaps one of the challenges is also around the data sets themselves, one of them in in particular being adverse event reporting. Now we hear over and over again that generics comprise close to 90 percent of the adverse events, but yet I don't think that that's reflected in adverse events both mandatory reporting and the voluntary reporting. And I don't believe it's a mandatory reporting issue. I think there's a lot of compliance and FDA enforcement around that. And perhaps we would all see that in, and there would be news about people not being compliant in that regard. But I think that maybe on the voluntary side, there's no regulation governing whether or not physician or patient reports to the brand or generic, and there could be

a lot of that going towards the brand, so you're not getting a complete picture. Not that there's a problem, but you're just not getting -- that data set's not accurate to begin with.

Does it make sense?

DR. LIONBERGER: Yes. Nilufer?

DR. TAMPAL: Just do address the concerns that you are raising -- and I'm talking from the review perspective. When we are talking about interactions, if it's related to the API, whether it is the generic drug or whether it's the RLD, the reference drug, if it's API related, then it's not formulation related. So it's nothing to do with the generic as such. If it's formulation related, just to stress on this, when we see differences in the profiles for the generic versus the reference product, we do evaluate further into that. And then if there are safety concerns -- say it's an epileptic drug and we see differences in the profiles -- we will further consult with our medical officers.

There are certain cases where we have even

used further modeling to see what would be the minimum concentration. Is the subject safety and efficacy, is that going to be affected? And if we find even from the modeling that that could be possible, then we wil further follow up with the applicant. We are very careful about -- like when we see differences in the profiles and when we have concerns about the safety, we do take additional steps, and that's regarding the formulation.

DR. ROSTAMI: Let me just clarify again, this is neither formulation nor the API. It is the fact that formulation is shifting. The way the API is getting absorbed is causing that particular issue. Because you have got a certain limit of tolerance for the bioequivalence, you will see the Cmax is still within the limit, Tmax is still within the limit. But because we have got a shift of the location of the absorption that is happening, now the interaction with the drug that is absorbing in a certain region more aggressively than other regions is going to be very different.

So I think that actually has nothing to do

with -- API is having the same interaction if they put them together, formulation with passing the bioequivalence. But because within that window of acceptance of bioequivalence, you are shifting the absorption in the GI tract, you are going to have an impact. And that is something that not many studies have done. As far as I know, there are only three examples. One of them we are actually publishing, [indiscernible] very soon, and the other one is the example that I showed that we are working on it, but it's not ready for publication yet. But none of these are intentionally actually studied. They are only coming from anecdotal data, and now we are supplying them with the modeling to show that, yes, this would have been making it from possible, saying that, yes, this would have been actually likely.

DR. HOCHHAUS: Do you see the possibility to catch those cases for in vitro studies? Because that's essentially the only way.

DR. ROSTAMI: Absolutely. That was my argument. Before, the whole idea of getting the

system right together with the in vitro, all the other experiments that [indiscernible] and others were saying, the whole idea is tool enable us with confidence to remove the ones that are possible, look into the ones that are likely without forcing everybody to go and do these studies in those situations because that is not basically affordable.

DR. LIONBERGER: I'd like to continue this discussion a little bit with asking people for any final questions they have on this application to the use of generic products in pediatric populations, specifically. That was raised in one of the comments.

Are there any specific research issues related to the use of generic products in pediatric populations that you think should be considered in the development of research priorities?

DR. UHL: I'll just echo I think what was said earlier, is the aspect os signal detection. I think if we're concerned that there may be some specific issues related to pediatrics, there's a

whole -- none of us are the experts sitting around the table here related to pediatric studies, pediatric ethics and all that kind of stuff. I think with the limitations that we have in the program, I think what we'll probably want to look for is how do we maximize signal detection in the pediatric population. How do we build off of any other systems that are doing all that kind of work: Wheter it's, Sarah, as you said, kind of the real-world evidence, or whether it's Sentinel, or whether it's other kinds of databases or or such. I don't know that we've spent a whole lot of time and effort even within the agency exploring that.

DR. SCHMIDT: I think we need to narrow this down a little bit because obviously pediatrics is a very wide space from neonates to 18 year olds, and we know, for example, that the absorption in neonates is changing very rapidly within the first days of birth. So if you're looking for an oral formulation, for example, then absorption changes quite significantly due to the fact that God is calling basically online. So I think these

physical changes, if you will, probably trump like any formulation issues that you would ever see, and I think a better understanding of these physiology changes in these very young children, but also the impact of cytochromes and phase 2 metabolism coming online and what sort of impact this may have on potential subpopulations that will react differently to a given formulation I think would be worthwhile.

DR. LIONBERGER: Sarah?

DR. DUTCHER: I just wanted to add I think the use of these large big data databases is an area where we can answer this question or at least work on this question, not only for pediatrics but for all populations where the physiology may be different that would impact absorption between a generic and a brand formulation. So maybe -- and the geriatric population has been mentioned or people with kidney or liver dysfunction. You can look at any of these subpopulations in these databases and try to see if you can see a signal. The methods for detecting the signal is another

challenge, but I think this is an area that can be worked on.

DR. LIONBERGER: So can we transition to some questions about what are any of the sort of scientific challenges that would impact the signal detection questions, especially as you begin to look to try to use things other than FAERS to identify or monitor successful generic substitution?

DR. DUTCHER: Rob's looking at me, so I guess I'm going to start. And I'm speaking just from the perspective of data, like secondary data like I mentioned, electronic health records and administrative claims. OG has learned under GDUFA I that there are some unique challenges to studying generics in comparison with brand that aren't faced by new drugs in terms of methods. For example, temporal confounding is a major concern. And I was thinking in the context of complex generics, which is a new topic under GDUFA II. There are actually some additional challenges that I think can be addressed or at least that need to be addressed.

So because these complex generics are now starting to be approved but under unique or unusual bioequivalence approaches, I think showing -- kind of proving that the bioequivalence approach worked by doing postmarketing studies is important and relevant.

I'm thinking that a lot of these products, kind of capturing the exposure might be more of a challenge. Typically, we think these solid orals are dispensed at the pharmacy. We can track them using NDC code. But for some of these complex products that may be, for example, administered by a healthcare provider in a healthcare setting and not dispensed at the pharmacy, they're a little bit harder to capture and may be distinguished brand versus generic. So the ability to do that in these type of data is important, and I think evaluating what we can and can't do is necessary, as well as capturing duration of use. Making sure people are on the product when we're evaluating for a potential signal is also a challenge again because you can count pills, and if someone's dispensed 30

pills, you make the assumption that they're taking it for 30 days, in general, with some caveats. But if someone's being injected, or if someone is taking their inhaler, or if someone's putting a cream on, how do you know that they're taking it? Can you make the same assumptions? Are there other caveats that you have to consider?

So I think there's some unique challenges for studying complex generics that necessitate some research.

DR. CHAZIN: Some of the things that are problematic with using these databases is they contain expected adverse events, the profile of what's in the RLD already. So trying to get at what's the difference in the generic and is it causing an independent effect is the question that we really need to answer because if you compare authorized generic versus brand versus generic over time and you look for a common adverse event, I don't know how you can distinguish even when people switch. And that's the problem I see needs to be more -- we need to get more research on what is the

formulation difference, does it have an independent effect, is it an excipient, and impurity, and its own effect, and then causing a safety issue that then we can detect, especially as a formulation becomes prominent.

So that's the kind of challenges that I think we need to shift to, to try to answer some of these questions.

DR. SCHMIDT: I think a physiological interpretation of the signal is also very important. To give an example for pediatrics, two examples come to mind, acetaminophen, which is very frequently prescribed, or morphine for pain management. In both cases you have active metabolites, which play an important role. So from a systems point of view, I think it would beg the question what is the rate limiting step? Is it the release from the formulation at which the drug or the metabolite becomes available? And then to what extent and at what rate is that metabolite being formed, and can it get to the site of action? So for example, glucoronides for morphine are not all

able to penetrate the blood-brain barrier. So I think it's a dynamic scenario.

DR. ROSTAMI: I think definitely I see a lot of value in the detection of these signals, but to me, once we did that, we have to go back, as Stephan was trying to show, and find the principles behind it, so we can build towards the recognition of the next one in advance, because by the time you are actually detecting these, that's too late.

At the same time, as he said, we can't -- because we have seen a signal come off it, all that particular group or all different drugs in that category needs to be now assessed clinically. So I think whatever that we do with the recognition of safeguards, signal, and assumptions that they're associated with it, I don't know, adherence is the same with the generic and the other one. Even people have paid differently for them, et cetera.

So I think at the end of the day, we have to go back and build a mechanistic model for understanding that what happened, and then try to come up with the rules that they are applying for

modeling whatever else that's going to fold into that particular parameter space.

DR. McNEIL: What I'll offer iS how complicated what we're discussing is at a molecular basis. So it's very similar to personalized medicine where if we give an oncology drug to a population, 20 percent will respond and 80 percent will not, and trying to go after that molecular basis of why those 80 percent did not respond when in fact you're using the same API on the whole population, that is a mult year, if not decade, project.

So I think that a first incremental step in finding a signal is understanding that signal may just be binary. Yes, there's a response; no, there's not a response. But attempting to go after the principles is a very ambitious project.

DR. ROSTAMI: I think I have to disagree because the reason for this argument is the majority of what defines are before what is in the body. So it is only the way that we are getting into the system. And getting into the system, the

majority of the elements we know, whether it is GI tract, whether it is the skin, we know, but we have to do the sensitivity analysis as we discussed this morning, identify those parameters, and see what are those parameters, how they differ between different populations. So we are not in a haystack looking for a needle. We are starting from a good position.

DR. ROBERTS: I'm just wondering if there's a sleeper here, and that's the placebo effect. In the old days, people used to argue that a small purple tablet was best for some psychotic condition; a red or yellow one was best for metabolic disorders. And I look at the generic products, and none of them have different shapes and sizes and colors to the reference-listed product. It doesn't matter, and I'm not convinced it doesn't.

DR. LIONBERGER: Mark?

DR. RITTER: I also tend to agree. One of the big issues we have that we haven't talked about is what are the signal detections based on

subjective reports? We have no objective criteria. We don't have a blood level. We don't have anything to corroborate what we're seeing. So this placebo effect, we have to take a patient's perspective and find a way to kind of tease that out, if there's a way when we're looking at these databases, and then we can start looking more objectively. And that is another huge challenge that we have.

DR. LIONBERGER: I'd like to change direction a little bit; not a lot, just a little bit. In Jeff's survey of new very complex products, what you saw in that was a lot of new complicated innovative drug-device combinations that raise a whole set of issues. So I want to start with issues related that link to this -- that are related to the patient use of drug-device combinations, and this can be -- I would like also -- some of these products where the nasal and inhalation products, the sort of new ones.

What are some of the challenges you see in developing equivalent standards, proactive

equivalent standards, for those types of more complicated drug-device combinations, focusing first on the patient interface? How do we figure out what needs to be similar for those types of products? So I'd like to open the discussion around that. So Julie?

DR. KIMBELL: I think it's probably going to be pretty important to assess whether or not patients are actually using the devices properly. From my experience, even a simple nasal spray is used in many, many ways, and I wonder if some of these more complex devices will be -- I don't know. I don't know how effective the communication will be in teaching patients how to use them and then how good the compliance will be.

So I think there's an important thing to consider going forward in terms of deciding if something is equivalent, a new product is equivalent to one of those established ones when they become established.

DR. LIONBERGER: Howard?

DR. CHAZIN: Yes, I especially echo that.

We have a lot of, let's say, generic sumatriptan out there with a lot of different injectors, and we get complaints all the time. A patient picks up a new refill, and it's a different injector, so they have to learn how to use it. And especially if it's something that's oral nasal, what if they suck on it instead of blowing. It's going to be very challenging, and we even have safety issues from just a different syringe with different markings that have caused safety problems or a different needle.

So these device-drug combinations, I think that we really have to pay attention to because there will be postmarketing safety if we don't get them right in the approval process.

DR. LIONBERGER: Is there anything that you learned from errors with the reference drug that ought to affect generic drug development or some way that you could look at that factor? I'll maybe ask the members from the generic industry here. As you're developing these products with more complicated user interfaces, what do you look at to

ensure, oh, I might have a difference from this product; I want to make sure that it's okay?

What type of research would help you make those design decisions more effectively?

DR. VALLANO: I'm not an expert in device development, but I think some of the things that we look at, you're looking at the fundamental operating principle of the device and trying to as closely align that with the reference product as you can. I definitely agree with what's been said, as this next generation of these more complicated devices come in, I think it's going to pose an extra challenge that we'll have to deal with.

MR. TANTILLO: I would just add how close is close? That's a big question, Mark, for you and for generic companies, and we struggle with that all the time. The more complex the device is, the bigger the issue is for us, obviously. I think that we look at conditions of use. We try and boil it down to conditions of use, and I think -- and I know it's easy for me to say this but difficult for you guys to kind of put it into research, but

certainly product-specific advice on these new complex drugs, maybe it's triggered when the NDA gets approved, it's obvious. You have a great definition of what a complex drug is; it's a device. Maybe around that tIme when we start looking at are there other human factor type studies, product specific human factor issues that need to be looked at.

Some of it's evident by just looking at the device. I have to say that. But in terms of how close is close when there's intellectual property wrapped around that brand that you can't penetrate?

DR. ROSTAMI: I was going to ask, out of my own interest, is how you actually define the goal post here? Eighty percent of population that you are testing should come up with the end result with regard to how they are putting the needle or whatever that they are doing with it, or you will be actually looking at the outcome, again, in the concentration profile because I am not sure of how you actually roll into your study, exactly I read it.

DR. LIONBERGER: So I would say the question for this meeting is not to answer your question on how close is close, but it's to try to formulate research questions that might help us answer the how closes is close questions.

DR. UHL: Actually, I've got to do that on both sides of my ears. My head's going to explode right now. But what I hear is human factors -- human factor studies are pretty much required for an innovator product when it's coming as a complex drug-device combination. So what I'm hearing is using some research realm to help establish those aspects of how do you determine sameness for these, whether they're engineering based, mechanical type studies, whether they're statistical approaches and things of that sort. Those are tangibles we can take back and try and formulate a research program or add to Rob's portfolio for the GDUFA program, investigating these sameness characteristics around these complex device delivery forms and something.

DR. ROSTAMI: This is a very naive way of

looking at it, but one way could be just not to instruct it more than what it is going to happen in the clinic, in the real world, and let that effect to come into the concentration effect profile that anyway we are measuring as a bioequivalence. If it's not making an impact, that is part of actually the modality for that. That's one. But as you say, this is a research project to look into.

DR. UHL: So for example, recently we published the -- I'm going to get this guidance wrong, but comparative human factors guidance. This is in conjunction with Office of Safety and Epidemiology, OSE. So while the docket is open, my ask would be for people to look at guidance and say, wow, I could see this, this, and this has kind of research studies that could be done to really help the agency figure out then how to come up with whatever these criteria of sameness would be. That would be really helpful to us. So thanks.

DR. BILUTTI: When listening to this, I think one really nice piece of research would be to

identify complex formulations which benefit from some sort of training device where I can do the procedure without the drug and then get a green light if I do it right or a red light if I do what I probably usually do.

DR. LIONBERGER: Let's try to move -- no more comments on drug-device combination related human interface related questions. Move on a little bit to the other side of drug-device combination questions, research related to the performance of the drug-device physical characteristics, drug delivery characteristics that may need research to establish, especially when you look at some of these newly approved products like some of the other performance as opposed to user interface issues for any of those drug-device combinations that were identified that you think maybe should potentially be on our research agenda.

DR. ROBERTS: Rob, a question, what do you do when you've got a product which is not very good in the first place, and you've got matching to that product. How are you ever going it out?

DR. LIONBERGER: The standards for approval of generic products are, in general, equivalence. It's not better. It's certainly not worse. You have to match the performance characteristics of the RLD. Although, I'd say there are some cases where the, in fact, standards are no worse than, an example, like impurities.

DR. ROBERTS: No, no. My message was in terms of the marketplace, you're not going to get signals back necessarily that this is any worse or better because it's got a very sort of murky sort of input anyway.

DR. LIONBERGER: That gets to the question of the signal detection questions that we talked about earlier about how to get the signal out of the noise. That's the case where you have more noise. Comments on that area certainly are welcome as well.

Celia?

DR. CRUZ: So I guess it will depend on the type of product, but we might need to identify these particular CQAs that are not just part of the

equivalence or performance of the drug in the body, but that have to do with the drug-device interaction, meaning if the generic changes, either the formulation or the device, the materials, how do we know that they've identified the correct specifications for that manufacturing ability and the quality control for that specific system just like an innovator would, and whether or not any of those ever raised to the level of something that would have to be product specific, or is it just specific to the quality controls of that drug-device interaction?

DR. SCHMIDT: For complex formulations, I think of formulations in general, the issue of batch-to-batch variability has been raised. I'm not sure if there's ongoing research, but that would be a suggestion, to look if maybe the innovator product has device-device variability and what sort of impact that would have on a potential generic.

DR. LIONBERGER: Can the generic industry comment on their thoughts on batch-to-batch

variability of reference products?

DR. UHL: And what kind of research we at the agency could do to help as you're trying to develop these products.

DR. VALLANO: Maybe I'll go first. I think that certainly we've seen with complex drugs -- and we've done a few -- batch-to-batch variability and the brand, and that's confounding to us because then where is our target, where are the goal posts? And that's a big, big issue for some generic companies. In terms of what research, the products out there, it's the brand. They're FDA approved. It is what it is, and I guess helping us understand what it is in terms of research might be -- if you're looking at these drugs -- the trigger for you guys of course is when the NDA's approved, and you start doing this focused research on complex drugs, part of it is the variability. I think that's part of it, I think, understanding batch-to-batch variability of the brand. That's the expectation for us.

DR. LIONBERGER: I completely agree. Just

listening to some of the discussions all day and some of the issues that were raised about slight formulation effects. Amin, you have a great example today, and just thinking about in the context of brand or lot-to-lot variability and how some of the same issues potentially could exist on different ends of the spectrum of the reference. Now, how that boils down into specific research for FDA to do, I think, just to echo what's been said, is trying to understand and help the generic industry understand how that affects the goal posts that we have to work within I think would be a very valuable endeavor.

DR. VALLANO: That's very helpful. Thank you.

DR. LIONBERGER: Now, as we move toward the end of our panel discussion, I'd like to open up to broader discussion. If there's any aspect of new areas that you've seen throughout the day today that you would like to flag to us to consider as potential research priorities or relative ranking of things that you think are more or less

priorities based on the overall concept, I think this is the opportunity to bring that out in this discussion here as a concluding point. specifically think are there things that should be added to our research agenda that you've identified throughout the discussions you've seen today. So I think that would be very helpful to us in going forward. So I'll leave that to the panel, to the audience, to provide some sort of ending thoughts on that particular question.

MR. TANTILLO: I have a thought -- could you share -- and maybe you've done this in the past. But could you share sort of what the industry or to the Federal Register, here's the list of priorities and here's how we prioritize them industry, world, and what's your thought on it? Because we make think that something in our minds might have a higher priority in our minds than you.

DR. LIONBERGER: We would consider that as a good comment to the docket. We've put out the last -- for the last year, we have 15 of those. We haven't put them in order. We love all our

children. But certainly feedback from the industry of saying these are the ones that are absolutely important to us now, and also these are the ones that are important for you to be working on now, but they're not critical. Work now, but the issues is five years. These are we're dealing with this today. That's also helpful to us. We're trying to also develop a portfolio, and that means having multiple -- looking not just for the long-short term, but long term.

MR. TANTILLO: It's like what Cook said. You've got a $trillion worth of research here, and you've got a smaller budget, so what in terms of priorities?

DR. UHL: I think part of what the agency does when we have public meetings like this and we have an open docket know is how frequently are we hearing similar comments and similar responses from external stakeholders, and how does that resonate with what we know internally, which may be proprietary and we can't share. And how we're able to match those up is kind of how we come up

with -- Rob has a list of 15, the top 15.

I would say at the end of the day, when you have this meeting plus a docket, there is easily approximately 100 type parts you would have. I think what Rob an his group has done over the years is a really good job of kind of bucketing them. So where there might be five or six that really fall into one bucket. The agency in our procurement methods, are complicated they are, contracts and grants such. Having ideas within buckets is actually very helpful as we go forward with procurement for grants and contracts because sometimes things fall through.

Does that kind of answer your question?

(No audible response.)

DR. DUTCHER: Can I add one more comment?

DR. LIONBERGER: Sure.

DR. DUTCHER So we were talking earlier about using these large databases to look at safety and efficacy, and somebody raised the point -- I forget who it was -- that sometimes these outcomes are really intangible and hard to capture in

claims. So one method that we've done research on in the past few years has been looking at switching patterns, especially switchbacks, which Howard mentioned in his talk.

I think that area is really useful, especially it's kind of unique to generisd. I think it needs more work, especially looking at switchback patterns. What are the criticisms I've seen of is what does it mean? You know, if a patient switches, they're such as back, how do we know that it's truly due to the, you know, an issue with the generic and not something else. So teasing that out, whether it be additional claims study is trying to look at hard endpoints or surveys asking patients why the switch back? I don't, I'm not sure, but I think that area needs some additional work as well because, especially it's unique to generics.

I think it needs more work, especially looking at switchback patterns, what are the criticisms I've seen. What does it mean? If a patient switches back, how we know that it's truly

due an issue with the generic and not something else. So teasing that out, whether it be additional claim studies trying to look at hard endpoints, or surveys, asking patients why they switched back, I'm not sure, but I think that area needs some additional work as well because it's unique to generics, and I think it's interesting.

MR. VALLANO: Just a couple of thoughts, I think one thing from an industry perspective that's important, looking at complex products, and this is an ongoing research initiative, but it's a development of, of in vitro models to predict immunogenicity of impurities. I don't know if you could comment on how you see that sort of effort shaping up. I don't think anything has been published yet.

DR. LIONBERGER: As we said in our update this morning, we have internal projects working on that, where we're reviewing the possibility of an external collaboration in that area as well. So we definitely think that that's a priority. That's an example of something that I think of as a long-term

priority, but definitely something that is important and sometimes is a barrier to generic approvals and challenge in product development.

DR. UHL: And I think for the agency that also involves bringing in people involved. For example, from OPQ, who really do that kind of work for larger molecule biologic type products who really have that expertise and asking are those the same methodologies that you can apply them for smaller molecules. Before we go forward and develop new stuff, are there parts that are well developed that are just as useful in this field.

DR. LIONBERGER: Scott?

DR. McNEIL: Just to add to already the very long list of things and recommendations, in the public comment, they talked about patient education. Maybe that's more pronounced at disadvantaged populations is what I gleaned from that. Maybe a very small project just to see if education can influence that and specifically at the level of the pharmacist, where the hypothesis would be an extra three minutes at the counter,

does that change anything that we see in generics. Just as I said, another recommendation for your long list.

DR. RITTER: I would just like to echo what Cook said earlier about the comparative human factors. Any suggestions, looking at the guidance out there and just providing some feedback is greatly appreciated. It's an issue that we all struggle with. Humans are not perfect. There's always going to be errors identifying those areas, critical aspects, to make a generic as the innovators, something that we want to get on the market. So any comments, we greatly appreciate it.

DR. BILUTTI: One thing I would be highly interested in, when FDA puts out your draft list of potential priorities, industry has a very different perspective. One thing which industry would be uniquely qualified to comment is which of those potential priority items would have the highest likelihood of cross-fertilizing. I saw this small project, another defined research area, but when you have 85 ideas how to apply it elsewhere, it

would be I think very valuable.

DR. LIONBERGER: We appreciate input from the industry into that type of question through the docket and through the industry working group meetings with FDA around regulatory science as well.

I think this is your last opportunity to make a comment here. The docket is going to be open for another 30 days for written comments, and then you will seeing the outcomes as we then digest this over the summer, and then the outcomes will be shared in the early fall. So seeing no further indications or the likes, I'd like to welcome Cook to give the closing remarks.

Closing Remarks - Kathleen Uhl

DR. UHL: Thank you. Thanks, everyone. Thank you for the nice discussions today. I really appreciate it and appreciate all the input from everyone. we had about, as my count, which is not accurate, but I counted about 100 people in the room, and I heard over 200 that were online. Is that about right? I think 240 or something. So

that's pretty good, and we're really happy that that number of people are interested in the GDUFA Regulatory Science program. And our office, OGD, is very appreciative of your interests, those here and those online, in this topic and on your engagement today.

The GDUFA Regulatory Science program fosters collaboration between FDA and our external stakeholders to provide tools that can assist anyone who is developing generic drugs. So those of you developing generic drugs and us, the agency, obviously, and efficiently evaluating and approving generic drug products, because at the end of the day, I think if we develop them but they don't come to fruition as a product that's approved, then we kind of haven't really done anything for the public health, and we are a public health agency.

We will carefully consider all the comments that we heard today as well as the submission to the docket, and as we develop the fiscal year 2019 regulatory science initiatives under GDUFA. The OGD, Rob's office, Office of -- I'm going to get

you wrong; I do that all the time -- Research Standards -- I always want to call it regulatory science. and I know it's wrong. After five years of this job, I still can't get that acronym straight. I was the one who pUt forward the reorg package, so that's really a problem.

Rob's office will put together this regulatory science, priority list for 2019. It will be presented to the center director, Dr. Woodcock, for her to endorse that priority list, and then it will be posted to FDA's website in early fall. So we are highly encouraging you. So to your comment about wanting to see the draft list, that's not the way we have worked on this. We would like your comments via the docket. The docket closes June 24th, so we strongly encourage you to submit any and all comments to the docket.

I want to thank all the speakers today, those from FDA, those from industry, and those from academia. These were invigorating and imperative presentations for all of us to hear and for us to hear your perspectives. Your input informs our

thinking and helps us identify opportunities and challenges as we make important decisions about where to focus our resources on research priorities.

I also want to thank the panel members, so those of you that are here this afternoon and those that were here this morning, and those of you that were here for both, especially, thank you very much for providing your perspectives on provocative questions and for introducing provocative questions, so thank you very much. The discussions that were held today will help us continue to develop a strong regulatory science program for generic drugs.

I also want to thank Rob, who earlier this morning I asked him if he would give my closing remarks, to which he said he would, but I've been able to hang in there all day today. Rob is our director of the Office of Research Standards, and he did a great job I would say moderating the session and facilitating engagement, engaging dialog, trying to solicit input again on the

current or actually its next fiscal year's research priorities.

I'd also like to thank Rob's group, ORS, all the ORS staff who were here in the room outside that helped with developing this program and facilitating everyone getting here and coordinating the entire workshop. I also want to thank Murewa Oguntimein for providing vital assistance with coordinating this workshop.

Murewa, where are you hiding? She's probably outside. You did an excellent job of ensuring that everything ran well today, both behind the scenes and in front, so it was a seamless day, so thanks, Murewa.

Again, I want to thank all of you who attended today and thank you for your feedback that you have provided us today. The FDA GDUFA Regulatory Science program has been and continues to be shaped by feedback provided to us from all external stakeholders at this annual meeting and as well the comments submitted to the docket. So we thank you again for your engagement, and today's

meeting is now concluded, so thank you.

(Applause.)

(Whereupon, at 4:03 p.m., the meeting was adjourned.)