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Session 2: Predictive Tools for Generic Product Development and Assessment

Co-Moderators:
Lanyan (Lucy) Fang, PhD Deputy Division Director, DQMM, ORS, OGD, CDER, FDA
Ahmed Zidan, PhD Senior Staff Fellow, DPQR V, OPQR, OPQ, CDER, FDA

- **Public Comment Presentations on Predictive Tools for Generic Product Development and Assessment**

- **Advancing the Use of Model-Integrated Evidence in Generic Drug Development and Assessment**
  Liang Zhao, PhD Director, DQMM, ORS, OGD, CDER, FDA

- **Integration of Simulation, In Vitro and Clinical Methods to Support Complex Drug Product Development**
  William Ganley, PhD Senior Specialist, Nanopharm Ltd. (an Aptar Pharma company)

- **Modeling of Locally Acting Drug Products: Identifying and Addressing Factors Affecting Extrapolation**
  Jessica Spires, PhD Principal Scientist, Simulation Plus

- **Digital Twins and In-silico Trials to Support the Approval Process of Complex Generics**
  Jan de Backer, PhD, MBA Chief Executive Officer, Fluidda

Panel Discussion

In addition to moderators and presenters listed above:

Public Panelists:

Robert Bies, PhD	Prof. & Assoc. Dean, School of Pharmacy and Pharmaceutical Sciences, Univ. at Buffalo
Clare Butler, PhD	Principal Product Development Scientist, Teva
Andrew Cooper, PhD	Senior Director, Mylan Global Respiratory Group, Mylan Pharma UK (Viatris)
Sivacharan Kollipara, PhD	Team Lead, Biopharmaceutics, Dr. Reddy's Laboratories Ltd.
Ping Zhao, PhD	Senior Program Officer, Bill & Melinda Gates Foundation

FDA Panelists:

Dhaval Gaglani, PhD	Supervisory chemist, DPQAV, OPQAI, OPQ, CDER, FDA
Meng Hu, PhD	Team Lead, DQMM, ORS, OGD, CDER, FDA
Rebecca Moody, PhD	Pharmaceutical scientist, OPQAII, OPQ, CDER, FDA
Zhen Zhang, PhD	Master Pharmacologist, DBI, OB, OGD, CDER, FDA
Liang Zhao, PhD	Director, DQMM, ORS, OGD, CDER, FDA

Jayanti Das, PhD	Research Scientist, DPQRVI, OPQR, OPQ, CDER, FDA
Bryan Newman, PhD	Lead Pharmacologist, DTP-I, ORS, OGD, CDER, FDA

Lucy Fang (FDA): Good afternoon, Welcome to Session 2: Predictive Tools for Generic Drug Development and Assessment. My name is Lucy Fang, and I serve as the deputy director of the Division of Quantitative Methods and Modeling, Office of Research and Standards, Office of Generic Drugs. I will co-moderate this session with Dr. Ahmed Zidan, who is a senior staff fellow from the Office of Pharmaceutical Quality Research, Office of Pharmaceutical Quality, FDA.

As you probably heard from this morning, the purpose of this workshop is to identify what research FDA should prioritize. We strongly encourage discussions on the current scientific challenges for generic drug development and ANDA assessment that will be addressed by the proposed research.

In Session 2, we will include 23 in-person and virtual 5-minute public comment presentations. After that, we will have 4 fifteen-minute faculty presentations on proposed research relating to modeling, simulation, artificial intelligence, machine learning, and novel ways to support demonstration of bioequivalence for inhalation products.

Before we get to the public comment presentations, I would like to first welcome our public panel members:

- Dr. Robert Bies, professor and Associate Dean, School of Pharmacy and Pharmaceutical Sciences from University at Buffalo
- Dr. Clare Butler, attending our panel session virtually, principal product development scientist from Teva
- Dr. Andrew Cooper, senior director from Mylan Global Respiratory Group, also attending virtually
- Dr. Jan de Backer, CEO from Fluidda
- Dr. William Ganley, senior specialist from Nanopharm
- Dr. Sivacharan Kollipara, team lead of biopharmaceutics from Dr. Reddy's, attending virtually
- Dr. Jessica Spires, principal scientist from Simulation Plus
- Dr. Ping Zhao, senior program officer from Bill and Melinda Gates Foundation

Thank you all for attending today’s session.

I would also like to introduce our FDA panel members:
- Dr. Dhaval Gaglani, supervisory chemist from FDA's Office of Pharmaceutical Quality
- Dr. Meng Hu, team leader from the Division of Quantitative Methods and Modeling, Office of Research and Standards, OGD
- Dr. Rebecca Moody, pharmaceutical scientist from Office of Pharmaceutical Quality
- Dr. Zhen Zhang, master pharmacologist from Office of Bioequivalence, OGD
- Dr. Liang Zhao, director of Division of Quantitative Methods and Modeling, Office of Research and Standards, OGD
- Dr. Jayanti Das, research scientist from Office of Pharmaceutical Quality
- Dr. Bryan Newman, lead pharmacologist from Office of Research and Standards, OGD

With that, I'm going to turn it over to Dr. Zidan to kick off the public comment session.

Ahmed Zidan (FDA): Thank you, Lucy, for the introduction and welcome to our session. We are going to start the public comments today with blocks of public comments alternating between in-person and virtual public comments. As Lucy mentioned, we have 23 presentations today.

We are going to start with the first public comment, and we would like to welcome Dr. Hong Yu, director of Regulatory Science, and Dr. Xu Chen Ma, VP of model-informed drug development and quantitative medicine from Critical Path Institute, and Dr. Sandra Sharp, president of Regulatory Strategies and Simulations, and Dr. Anuj Jofan, professor at Colorado School of Mines.

Huong Huynh and Shu Chin Ma (Critical Path Institute): Thank you to the organizers for inviting Critical Path Institute to present this public comment. My name is Huong Huynh. I'm Director of Regulatory Science at Critical Path Institute. I am here with Shu Chin Ma, VP for model-informed drug development and quantitative medicine.

I want to start by telling you about what Critical Path Institute is. We are a nonprofit public-private partnership that started in 2005, following the critical path initiative set out by FDA to accelerate medicine product development. What we aim to do is develop new evaluation tools that can be used to optimize clinical trials as well as tools that can help us accelerate drug development. By doing so, we hope to de-risk the drug development paradigm and process for industry partners, but also increase confidence in the review process because we aim to generate drug development tools that can then be endorsed by regulators for use in drug development programs.

What we do is convene public-private partnerships or consortiums made up of various industry stakeholders, academic researchers, including those from NIH. We have partnerships and participation from international global regulators as well. Most importantly, we invite patients and patient advocacy groups to participate in the discussions. The discussions we have are pre-competitive, so we are not talking about any one particular product, but in the pre-competitive space. By the time we get an endorsement of the tools, it is made publicly available, and everybody can interrogate and start using those tools.

We want to develop drug development solutions for regulatory decisions, whether by industry stakeholders or by the regulators themselves. What we have been able to do since 2005 is develop drug development solutions in such a way that we could help revisit labeling to see if there are modifications or expansion of labels that can be added based on additional data and science collected over time.

We don't really do CMC, so mostly what we have been able to focus on is using animal studies to help predict first-in-human doses. We also participate and help generate solutions in the clinical study area where the modeling simulations we develop can help determine the safety of the drug product as well as help the dose-finding exercise for use in clinical studies.

Through bioavailability modeling simulations that we've been able to develop, we can help optimize formulation as well as assist in determining the appropriate or best route of administration and optimizing the dosage form itself.

Throughout our history, we've been able to develop these solutions that have been used mostly in the new drug arena. But we also want to take the opportunity to raise the possibility of the

Office of Generic Drugs working with public-private partnerships to extrapolate and utilize these solutions for the development of generic products.

What we know right now is that there are multiple challenges that are foreseeable. The use of model-integrated evidence can be used to help PK/PD studies. We understand that modeling can help us understand better the exposure-response relationship. We also can use modeling to inform us in terms of transdermal performance and PBPK examples as well.

Fluid dynamics models can help us quantify the plume pattern of products as well as the spray angle. What we would like to encourage is the use of modeling to help us better understand drug function.

Some of the challenges in IVIVC include bio-relevant dissolution. It comes to a point where there needs to be taken into account the drug dissolution and distribution, the ADME characteristics of a drug product. However, we also recognize that there are inter-subject variabilities when it comes to animal studies as well as transferring that into patients or healthy subjects in a bioequivalence study.

I also want to mention AI and machine learning in terms of data analytics. What we would like to get to is using AI to help train and automate machines to sort through the noise. I know there have been talks over the years about big data, and I know FDA has a lot of data. Now, with drug development coming in with a lot of digital and electronic data, we need to get through that noise, so AI/ML can help us navigate that.

Lastly, on virtual BE simulation, we've heard about it this morning, and the importance is using real patient data, masking it so that we can then have synthetic data and create virtual patients. This can help de-identify the actual patients, but also having synthetic data to help the machine or algorithms learn.

What are the potential applications of quantitative solutions? On the left side, I've listed a couple of the challenges that we know are currently facing in terms of reviewers and drug developers. I wanted to focus and mention the clinical pharmacology perspective, the PBPK modeling perspective, the use of VBE simulation, and most importantly, the data analytics, which gives rise to several opportunities listed on the right.

Ultimately, I want to propose that the potential applications for quantitative solutions in the generic drug realm can be for the use of federated data that can then help generate drug development tools. We can also use validated quantitative models from already approved products as learning to develop new models for new products. We can also develop a framework so that we can educate the scientists as well as the reviewers, so that we can then also share the validated models. It's iterative learning.

From there, we could certainly learn from published data that's available and also from data of similar drug classes. All of this is iterative learning to then go back and optimize what we've generated before. There's also the safety monitoring aspect as well.

Thank you for your time.

Sandra Suarez (Simulation Plus): Good afternoon, everyone. It's a pleasure to be here. I'd like to thank the organizers for the opportunity to present today. Dr. Rash mentioned just a month ago in his introductory speech about the center for quantitative medicine that FDA is at the

forefront in advancing modeling and simulation to inform review and policymaking. One of these modeling approaches was physiologically-based pharmacokinetic modeling.

This slide shows that we have seen an exponential increase in the number of publications of PBPK applications in support of drug product quality, increasing from about 250 publications in 2021 to about 250 publications in 2022.

We are familiar with presentations that have alluded to the fact that PBPK has been widely used in support of drug development, especially for internal decision-making such as formulation selection, but also for regulatory decision-making such as setting specifications that are clinically relevant not only for dissolution but also for CMAs and CPPs. In certain failure modes, and even more importantly, PBPK has been used to support bio-waivers following major changes, specifically when a safe space has been developed.

I would say that this increase in the number of publications was highly related to the publication by FDA in 2020 about the use of PBPK in support of drug products. I'd like to analyze two recommendations given in this guidance.

One has to do with the use of non-BE data to demonstrate the model's predicted performance, and the other is the use of validation criteria which, according to the guidance, should comply with the IVIVC guidance published in 1997.

I would say that these two recommendations are highly impacting how these models have been approved and in terms of the deficiencies that are being highlighted by several FDA speakers.

For example, in 2023, Dr. Fang Wu mentioned that one of the common deficiencies has been that the model has not been approved because of the lack of non-BE data to challenge the PBPK model. In the same conference, Dr. Kimberly Lorraine mentioned in 2023 that one common deficiency observed in the probability of these models is inappropriate model validation.

I think one of these reasons is contributing to the lack of or low rate of approvability of these models, which is about 48%, and this rate is no higher than the one observed for non-mechanistic models.

Based on this, I think there is a need for research to determine the appropriate criteria for model validation that is applicable to PBPK specifically. Models that are IVIVC and IVR-based, because meeting the PBPK-based validation criteria of about plus or minus 10% that is described in the guidance is challenging.

Another thing that is very important to consider to move forward the field of PBPK in support of quality is the need for non-BE data to confirm the predictive ability of the model is challenging and could restrict the model application.

This is restricted and therefore limiting the probability of PBPK. As you may know, current practice safe space applications are limited to interpolation between non-BE batches, and that means that the application of the safe space could be very limited.

Therefore, I think there is a great need for research to evaluate the risk for model extrapolation beyond the knowledge space, and by knowledge space, I mean the data that has been used to develop and validate these models.

Dr. Fang this morning presented the application of PBPK in support of BCS class 3 bio-waivers. But I think when it comes to model validation, we don't know, especially when there is not enough data, when we are extrapolating outside the safe space, because extrapolating outside the safe space or knowledge space is something that FDA and other authorities are not open to, especially for extended-release formulations.

The question is, once the model is approved and we have built a safe space, in which situations is it possible to extrapolate with low risk? Again, Dr. Fang mentioned extrapolation of this safe space using a BCS class 3 drug. I think we should conduct research about what data are needed and how far can we extrapolate with confidence.

Also, I think this research would be very useful for expanding the BCS class bio-waivers, especially when it comes to, for example, if similarity testing is failing, if dissolution is failing. I think they would be important even when excipients are being changed, because the models that have been mentioned before, if they are validated, will be very useful to move the needle when it comes to bio-waivers for especially BCS class 3 and 1 drugs.

Thank you.

Anuj Chauhan (Colorado School of Mines): Hello, everyone. My name is Anuj Chauhan, and I'm a chemical engineering faculty at Colorado School of Mines. The title of our presentation is "Modeling Optimum Drug Delivery from Solutions, Complex Formulations, and Devices."

The basic idea of physiologically-based pharmacokinetic modeling is that you essentially start with mass balances, which means you look at all your unknowns and you write differential equations for all of those. That requires all the inlets and all the outlets to the tissues of interest. That's the basic premise with which we start pharmacokinetic modeling.

In the eye, the eye is actually a very interesting organ because, in some sense, all the inlets and outlets are very precisely defined. So PBPK modeling is a very useful tool for understanding drug delivery to the eye and establishing bioequivalence.

I'm going to keep my model very simple. The full model is more complex, but I'm going to look at only the most important equations.

Here's a schematic of an eye. You can see that when you put the drug in the eye, you put it as an eye drop, or if it's a device, you put the device here. In either case, the drug goes into the tears, and from the tears, the drug can go to the cornea, which is where you want the drug to go. But also, every time you blink, you're clearing some of the fluid through these openings called puncta to these tubes called canaliculi into the nose.

The conjunctiva, which is the other membrane in the eye, can also have transport across it as well, so all of those have to be taken into account as you write the mass balance equations. Interestingly, you write an equation for the drug, so the drug accumulation is balanced by all the inlet-outlet pathways. But you also do it for the tears because every time you're blinking, you're also pushing the tears out of the eye, and that is somewhat of a unique circumstance in the eye.

You write these equations for the tears, but you also write similar equations for all tissues of interest. Typically, when you're looking at ocular drug delivery, the concentration in the aqueous

humor is a surrogate marker. In addition to that, you can do similar equations for the back of the eye as well.

The tear drainage, which is the rate at which you push tears from the eyes to the nose, is actually very important because when you're blinking, you're essentially clearing the drug that you're putting into the eye into the nose. Once it is cleared, it's useless. You want to slow down that process. Many companies are developing different formulations which simply slow down the tear drainage.

What we have developed is a mechanistic model for predicting tear drainage, so it can predict the effect of all formulation parameters, including viscosity, surface tension, and concentrations. Therefore, you can use this model to essentially predict at what rate drug will be cleared from the eye. That's a very useful property to have or equations to have to essentially design formulations that will stay in the eye for a longer time.

Also, the eye has not just the cornea but also the conjunctiva. The conjunctiva is the membrane behind the eyelid, and the conjunctiva is very interesting because, in addition to passive diffusion, you also have ion channels there.

If you really want to do a more thorough model, you have to take transport through these ion channels into account as well, and that is important because ocular formulations have different counterions. Depending upon the properties of the counterions or the type of counterions, that could affect essentially the water transport. So that makes the problem somewhat more complex but also more interesting.

We have developed mechanistic models for all of these. My recommendation to FDA is to essentially support more funding for understanding the effect of all of these different parameters, including viscosity, salt concentration, salt type, on the transport in the eye.

We have all these model equations. In addition to essentially, even when you're instilling a single drug, you have to take into account all the counterions in the formulation because the transport of those counterions actually impacts the drug transport.

We write all these equations and then solve them. They can be solved using any software, including MATLAB. We have a lot of different validation. I'm going to just show you some very critical ones. We have calculated the drainage rates every time you're blinking - how much tears you're pushing from your eyes to your nose. You can calculate that using these equations, and that is within reasonable agreement with the model for both rabbits as well as other animals.

We also look at if you put tears and if you put a drug formulation in the eye, how long does it last before it gets cleared. We have done that, and here's a comparison for that.

Everything that I talked about today is basically about solutions. But really, a lot of drug formulations are not solutions but complex formulations. That means they're either emulsions or suspensions. In that case, the equations become slightly more complex because you also have to take into account the concentration of drug inside the emulsion drops or the particle size of suspensions. Not only that, you take into account the distribution of the particle sizes, so all of that can be done, and the equations are very briefly described here.

For emulsions, essentially you have to start keeping track of the concentration of drug inside the oil phase, and that basically requires knowing some other parameters for the emulsions like size

distribution and also partition coefficients. For suspensions, again, you have to take care of the size of the suspension particles because that will change with time. But again, all of that can be done within the context of the equations that I've already shown you earlier.

Another very big area of research for us is devices. We're looking at a lot of different devices - how you could put them in the front of the eye or the back of the eye. Our goal is that we should be able to characterize the devices in vitro under perfect sink conditions and then separately, if you know the anatomy and physiology of the eye, you should be able to predict the drug distribution once you put the device inside the eye.

We've done it for a lot of different devices. I'll just show you today's work for contact lenses. Contact lenses are very interesting because once you put a contact lens on the eye, what happens is the contact lens releases drug directly over the cornea. This is much superior to eye drops because you can get a much higher fraction of the drug going into the cornea and aqueous humor and other tissues.

Today, I'll show you essentially how we can model this. What we do is we design a contact lens for drug delivery. We measure its release under sink conditions, and using that, we can completely predict the drug distribution after you put the contact lens inside the eye.

These are just the equations. These equations become more interesting because, in addition to the ordinary differential equations for all the tissues, you also have a partial differential equation that describes the drug release from a contact lens.

Finally, we can see that in this case, I've shown you a validation of the results. I'm showing you data for four different tissues - cornea, sclera, retina, and vitreous humor. In this case, without any fitting parameter, you can see that we can accurately, well within the error bars of the experiment itself, predict the concentration distribution in different tissues without any fitting parameter, purely physiologically based.

With that, the summary is that we think PBPK models are extremely useful for every approach for drug delivery, but especially for ocular applications, because all the pathways are very well characterized and can be measured in vitro and in animals.

The parameters are extremely critical. You can get them from animal data. You can also do some of your own experiments in vitro to actually get those parameters. Finally, validation is very important.

To finish, the suggested research topic that I have is to enhance the efficiency of bioequivalence approaches for complex formulations using essentially PBPK modeling for ocular applications. Thank you very much.

Moderator: Thank you, Dr. Hong, Dr. Sandra, and Dr. Anuj for the nice presentations. We have a couple of minutes to take questions from the panels and from the audience as well.

Clare Butler: Thanks everybody for your presentations. They were really informative. My first question is for Dr. Anuj. Very interesting presentation. Thank you very much and very clear. I would just like to ask a question with respect to the validation of your drainage rate model, and that's with respect to your in vivo experiments. If any have been done in humans, or are they all animal-based studies in terms of the comparisons that you have generated to date?

Anuj Chauhan: Great question. The modeling is obviously applicable to both animals as well as humans. The only question is the availability of the parameters. Some of the comparisons for the drainage rates are with humans as well, because those are relatively easy experiments to do in humans. All you have to do is take images of the fluorescence, and you can compare the decay. So yes, some of those have been validated with comparisons with humans as well.

Clare Butler: What level of variability do you see in the in vivo experiments?

Anuj Chauhan: There's considerable variability. The challenge, of course, is that the parameters - it all comes down to the parameters, right? Because ocular parameters are variable. For example, the permeability of water across the ocular membrane will be variable. Certainly, the active transport becomes even more complex. The challenge with all modeling is really the models themselves are obviously great, but how do you get the parameter values for those? That's where I think there's a lot of variability, which is reflected in experimental data. But there's not that much data. I really believe that FDA should prioritize looking at the drainage rate modeling because ultimately that affects the bioequivalence really very strongly in the ocular drug delivery space.

Markham Luke (FDA): The modeling is really interesting. The tear ducts drain into the posterior lateral nose, right? And back there, we also know we're studying this nose-to-brain model. Have you taken into consideration the eye-to-brain model as well? Because if something drops into an eye that can, if something is neuroactive, that could potentially have a neuroactive component. Are you doing any modeling to look at that in conjunction with the nose-to-brain part of the modeling that other people are doing?

Anuj Chauhan: Not really, because if you think about the pathways through which it can go from the drug to the brain, most likely it could be via vitreous humor, and from there, it's connected to the optic nerve. When you look at when you deliver drug via eye drops, only a very small fraction of the drug goes to the vitreous humor. So I don't know if that's really a viable path for delivering drug to the brain. But certainly, if you're putting a device into the posterior chamber, like any of the drug delivery devices, those could potentially be targeting the brain, although I still think that clearance is too high to really make it a viable approach.

Moderator: Thank you. We can move now to the second session, which would be a section of virtual talks.

We are going to start with Dr. Lavendra Singh. Dr. Singh is director of Pharmaceutical Systems Engineering at Rutgers University.

Lavendra Singh (Rutgers University): Hello, systems engineering, including the digital twin, is very helpful for generic companies as well. Today, I'm going to briefly explain how the digital twin model could help generic companies to adopt new developments in that area.

These are a few ideas. The first idea is that we need to develop adaptive models for generic drug substance and product manufacturing, including injectable manufacturing and oral solid dosage forms.

We also need to have advanced monitoring and control systems for real-time quality assurance, and the Industry 4.0 framework, including methods and software tools, will be helpful for generic companies.

We could also have advanced manufacturing processes for generic companies that are economically feasible. These ideas could help generic companies. As we know, generic companies have fewer resources to spend on R&D, so digital twins can help to conduct some of the R&D virtually.

This digital twin can also help to develop processes and products with less time and resources. Obviously, this work will help to assure product quality, and it could also help to solve some issues like quality issues and contamination issues in API and products.

This also helps generic companies to act fast, such as during pandemics or wars with other countries. Finally, it will help to bring generic manufacturing back to the USA with less time and resources.

There are many applications for generic companies. The digital twin is a kind of virtual experimental platform, so you can do many things, including design of control systems, process optimization, risk assessment, and so on. This can also be used for digital regulatory evaluation. Finally, it will be a knowledge visualization tool that can be used for training purposes.

These are three applications of the digital twin. Basically, at the top, you can see RTD-based control systems. This control strategy you can use to develop drugs and product types - injections, tablets, and so on.

Since tablet presses, for instance, are the same in both generic and branded companies, this methodology can be used for generic companies as well. At the bottom, you can see an example of real-time applications of artificial intelligence and machine learning models.

These methods and tools can be used for generic companies as well. Similarly, process models and other modeling approaches can also be used.

Here you can see the injectable drug product manufacturing line, and at the bottom you can see the digital twin. The digital twin, as you can see here, is a kind of exact representation of the pilot plant in the digital domain that you can use for digital experimentation.

Finally, process control is very useful for real-time quality assurance. If there will be real-time quality control, then it means there will be less burden on regulators, and also patient safety will be much more secure. So this is really essential.

Finally, I would like to thank you, and if you have any further questions, please feel free to contact me. Thank you.

Moderator: Thank you, Dr. Singh. We can move to Dr. Sebastian Polak. Dr. Sebastian is a senior advisor working for Certara UK.

Sebastian Polak (Certara UK): Today I want to quickly discuss and better understand what is needed to make predictive models accepted for regulatory decision-making. I would like to focus on complex generics.

The title of the presentation has been borrowed from a recent paper published by Markov, where it was very clearly pointed out that all models are wrong, and those which are not in use are actually useless.

The perspective presented in this paper was very much focused on clinical use. However, the key observations we see here - successful models are linked to actions, which is probably the most important one - have their meaning in the area of drug discovery and development.

One part of this paper is a checklist for useful clinical prediction tools. When I was going through this paper, I realized that the models which I want to discuss today, which we are using in drug discovery and development specifically with focus on complex generics, meet all the expectations and requirements listed in the checklist.

Here are a couple of examples of those models which are actually useful, not only validated but also useful. The simulation of virtual patients allowed waiving hundreds of clinical studies with almost 400 individual label claims and approvals. In general, predictions using, in this case, simulators allowed waiving multiple clinical trials, and it was applied for more than 100 novel drugs already available on the market.

What is important is that the area of application and type of problems solved by these models is very heterogeneous. There are multiple types of applications, including drug-drug interactions, food effect, special populations like cancer populations and pediatric populations. However, only two of them, as far as I'm aware, focus on complex topically applied drugs.

The first one - a PBPK model was used to assess drug interaction in a pediatric population, and in the other one, a PBPK model was used to waive a PD endpoint study with diclofenac being the drug of interest.

Two other applications I mentioned were based on the use of a dermal model which has been under development for more than 10 years, widely accepted and thoroughly validated, as proven by multiple publications and case studies available in the public domain.

There are also other routes of administration for which PBPK models have been developed and validated with thorough description of all assumptions and equations used for model building. In this case, I have in mind vaginal and rectal absorption models which are available in the Simcyp simulator.

To conclude, PBPK models are widely accepted tools which can be saved as model master files. They have been thoroughly verified and validated. They offer currently the same level of quality control as alternative models. They have been utilized in various areas to solve real-life problems and answer sometimes very complex scientific questions.

Considering that the complex generic area requires new tools to support development and successful submissions, the question arises: what is required for wider acceptance of PBPK models for regulatory decision-making?

The question which I would like to ask - I'll be very grateful for discussion during this meeting. Thank you very much.

Moderator: We can move to Dr. Maxime Le Merdy. Dr. Maxime is associate director of research and collaboration at Simulation Plus Incorporated.

Maxime Le Merdy (Simulation Plus): Good morning, good afternoon, good evening, everyone. My name is Maxime Le Merdy, and I would like to make a comment on behalf of Simulation Plus.

To provide some background, Simulation Plus has been an extensive partner with FDA to develop and validate PBPK models to support development and regulatory assessment of complex generic products.

Over the last 10 years, Simulation Plus has been working on multiple PBPK models for multiple routes of administration. You can see on the slide that we are currently collaborating on ocular, oral cavity, pulmonary, and dermal PBPK models. We also work on the impact of GI diseases on the absorption of APIs, how to use PBPK models to support the development of modified release formulations, how to develop workflows for virtual bioequivalence analysis, and finally, long-acting injectables.

All of the work being done as part of this collaboration is being published to support the field and share knowledge with the community.

The first comment I'd like to make is regarding budget allocation. In the previous grants I've mentioned, Simulation Plus has developed multiple industry and academic partnerships with universities, either abroad like the University of Bath, or in the US like the University of Connecticut or University of Florida.

A typical project in collaboration with one of those universities with the end goal to enhance and validate PBPK models to support complex generic products starts with the same issue: there is a base of published literature data that is typically not sufficient to fulfill the global project.

Therefore, in partnership with the academic partner, new in vitro and in vivo experimental data will be generated. Those have a certain cost.

For those collaboration projects, the budget is allocated as such: the money comes from FDA and is divided between Simulation Plus and our academic partners. For Simulation Plus, all of the money received is being used to support the research project. The money that will go to the university will have to pay some admin costs, and therefore only a percentage of the received money is being used to support the research project.

The main challenge that we are facing is that the complexity of PBPK models is increasing drastically, and to support the development and validation of models, we need to have access to new data.

Therefore, we ask our academic partners to generate new in vitro and in vivo data, which increases the associated cost for them. Because the budget is limited, we sometimes cannot do certain studies, or we have to limit the data sets or the sample size, and that can have a direct impact on the research project outcomes and conclusions.

The solution we have in mind would be for FDA to increase the budget, especially to support us and support these projects in generating new and more in vitro and in vivo data. With those data, we could then have a full investigation of all facets of a particular issue.

The second point we'd like to mention is how to use new in vitro data to support complex products. I think it's well understood that there are many new in vitro data being developed - 3D cultures, organ-on-chip, etc. - and combining the in vitro data with in silico models to predict in vivo situations is probably an interesting aspect for generic drug development.

What we recommend is to finance the development of new useful technologies combined with PBPK models to perform in vitro-in vivo extrapolation, and also to define what would be the role of these new technologies and what could be their impact on the development and regulatory assessment of generic products.

With that, thank you very much, and I wish you great discussions.

Moderator: We can move to Dr. Stephen Schmidt, professor at University of Florida.

Stephen Schmidt (University of Florida): Hello, everybody. Today I would like to share my perspective on how model-integrated evidence approaches can be used to support demonstrations of bioequivalence for long-acting injectables.

Before I do, I'd like to make a couple of general remarks about long-acting injectables, which are also referred to as LAIs. LAIs provide sustained drug release over a period of days to months. They're intended to increase patient adherence and reduce adverse events. The problem is that long-acting injectables are expensive, and oftentimes there are no generics available, at least as of yet.

Depending on the LAI, there are different approaches that can be used to demonstrate bioequivalence between the test and reference products. This typically involves bioequivalence studies, either alone or in combination with in vitro drug release testing. The problem here is that clinical bioequivalence studies can be long, depending on the LAI - ranging from months to years. The second problem is that there is typically a lack of in vitro methods that can be used as a surrogate for in vivo drug release.

I'd like to briefly talk about an example to showcase how model-integrated evidence approaches can be used to answer exposure-response related questions using levonorgestrel as an example. In this example, we used a combination of different modeling approaches consisting of a model-based meta-analysis approach, a physiologically-based pharmacokinetic modeling approach, and a real-world evidence analysis to make inferences about the impact of drug concentrations on the efficacy and safety of hormonal contraceptives.

We started with a model-based meta-analysis approach to characterize and predict changes in unintended pregnancies with increasing doses. Unintended pregnancies are expressed here in terms of Pearl Index.

Once we had this, we translated this into an exposure-response relationship using a PBPK approach under various conditions - either in healthy women with normal body weight or evaluating the impact of drug-drug interactions or a combination of drug-drug interactions with increased body weight, and seeing how this impacts our exposure-time profile relative to therapeutic target thresholds.

Once we had established this model for oral contraceptives using implants' in vivo release data over time - implants were taken out of women over time, and the amount of drug remaining in the formulation was measured over time to fit an in vivo drug release model - we used this in

vivo release curve as the front end to our PBPK model, which was then used in simulations shown here as black solid lines and overlaid with observed clinical trial data. What we can see is that we were able to predict what's happening clinically quite well.

A couple more notes: we were able to capture the average profile as well as the variance quite well. You see that concentrations here, not surprisingly, go down over time, and as they do, the frequency of unintended pregnancies goes up, which is not surprising because systemic exposures are lower after implant administration compared to oral contraceptives.

What does this have to do with long-acting injectables? I believe that we can now use this model-informed or model-integrated evidence approach developed for implants as a reference point for long-acting injectable hormonal contraceptives.

Here's what I think we should do: the use of model-integrated evidence approaches to assess bioequivalence for long-acting injectables can be used based on information of PK/PD across formulations. Specifically, I believe we should conduct a series of in vitro tests which are capable of recapitulating in vivo drug release profiles, using implants as a reference point, implement the in vitro dissolution profiles into a PBPK modeling framework to predict and compare long-term exposure in virtual bioequivalence trials and assess the impact of variability on both pharmacokinetic and pharmacodynamic responses, evaluate and confirm the generalizability of the proposed modeling framework using a second, typically long-acting formulation, and then ultimately conduct virtual bioequivalence trials to inform optimal trial design and dosing regimens.

With that, I thank you for your attention.

Moderator: With that, we will move to our next round of in-person public comment presentations. We will start with Dr. Elad Berkman, who is CTO and co-founder of Phase V Trials.

Elad Berkman (Phase V Trials): Hi, everybody! It's a pleasure to address this audience. A word about myself and the company: Phase V is a company that's building software for the design of adaptive clinical trials and for analysis of trials using causal machine learning, bridging the gap and using machine learning and AI to design better trials. I wanted to speak briefly about the opportunity of using adaptive trials for bioequivalence.

Just a word about adaptive trials - slightly different from most of what was presented here. The basic idea in an adaptive clinical trial is to leverage the data during the trial as it's collected to make better decisions. This has the potential to improve efficiency, potentially including fewer subjects in the trial. Or if we maintain the same number of subjects, we can improve the power. In certain cases, it has the potential to decrease time to market by stopping early, either for futility or for efficacy.

Most importantly, I think, for the world of generic drug development, is that it removes a lot of the guesswork. One of the huge challenges in generic drug development is that there are parameters that are very difficult to estimate a priori. When we start the design, we're actually making an informed but still a guess about what those parameters are going to be, and those parameters have a huge impact on the probability of success of the trial. Using adaptive design has the potential to mitigate some of that issue.

I'll speak about adaptive trials for generics. Adaptive trials for generics are slightly different and tend to have smaller sample sizes, which poses a challenge. We are trying to reach statistically valid conclusions based on a very small sample size.

On the other hand, the cost and impact of every additional patient is even larger in the world of generic drug development than in new drugs. Most trials are crossover trials where we have intra-person or intra-subject variability, and that's a key parameter with substantial uncertainty that's very difficult to estimate a priori.

It is often the case that there is relevant data - historical data that can be modeling data - that could potentially be incorporated using a Bayesian design into the trial.

The last point is that most adaptive trials today are still done with a very bespoke approach, which is very resource-intensive. What we're trying to do as a company is build tools that allow doing that in a much easier, more intuitive, and accessible way that would be able to support many more trials at a reasonable cost.

The topic of adaptive trials in the world of generic drug development and for bioequivalence specifically has been researched in the past. I think the seminal paper from Diana Potvin from 2008 suggested a number of different designs, but interestingly, there has been much less follow-on work. There has been an additional paper in 2016 that looked at optimizing those designs, pushing the efficiency of those trials. There's a recent paper from 2022 that Novartis published, actually looking at long-acting injectables where they expanded some of those capabilities to the world of parallel design, not only crossover design.

But as you can see on the right, the top panel shows the number of papers and citations of papers on adaptive trials, and that's two orders of magnitude more than what we see in the world of bioequivalence adaptive design. So we posit that there is huge room for investment here.

A recent example, and very exciting to see the people here in person, is adaptive and mixed-scale bioequivalence studies. This is a recent paper published by FDA looking at combining mixed-scale bioequivalence with an adaptive design based on that seminal paper.

Just looking at that sort of design, there are many degrees of freedom. How many patients we want in the initial phase of the design, how many replicates we want - this is an RSABE study - so how many replicates we want per patient, and where we have alpha spending between the first interim and the final analysis, what the optimal allocation of those would be, and what value of geometric mean ratio we'd like to assume for the trial. Those have impact on the trial design.

At Phase V, we've actually looked at a number of these parameters and built a mechanism that is able to find good parameters that ensure type I error preservation in a very efficient way, reducing the amount of simulations required by over an order of magnitude. We're actually working at the moment on building a mechanism to optimize those parameters for generic drugs in a very efficient manner using machine learning. So that's very relevant for this problem.

I'd like to end by saying that we feel there is substantial room here for further innovation in terms of adaptive trial design for bioequivalence, looking at additional types of adaptations, not only group sequential design and sample size re-estimation, looking at optimal designs and looking at what parameters ensure optimal designs.

Finally, and this is also very close to what we're doing, building blocks that allow doing this in an intuitive, easy manner, so that it's much easier and cost-effective to design adaptive trials for generics and doesn't require a bespoke process.

Thank you.

Moderator : we actually have the room for a couple for question form panel members. Anyone would like to ask a quick question to Dr. Berkman?

Question: Thank you for the very nice presentation. Is there any way, or do you have in thinking, how can we use real-world data to reduce the number of subjects for bioequivalence in terms of the schedule? Is it a viable option?

Elad Berkman: That is actually an area that is very relevant for Bayesian design. We can formulate priors using that historical data, and we can incorporate that in the trial to decrease the sample size. We can also do that in a way that is robust to cases where the data is less representative. So we can actually have dynamic weighting of the historical data. Those are things that are actually common - well, not common, but are acceptable in the world of new drug design, and I haven't seen an application in generic drugs, but there may well be.

Moderator: Thank you, Dr. Berkman.

We will move to our next talk, which will be delivered by Dr. Sebastian Melgar, a lead associate from Booz Allen Hamilton.

Sebastian Melgar (Booz Allen Hamilton): Hi, good afternoon. My name is Sebastian Melgar, and today I'll be discussing the utilization of artificial intelligence and machine learning in post-market surveillance, safety, regulatory review, and pharmacokinetic modeling for generic drug development.

The agency should consider prioritizing the use of AI and ML. During my presentation today, I'll be summarizing salient generic drug development challenges, potential AI/ML uses to address these current challenges, overview the considerations for implementation of AI/ML, and close with some recommendations.

Artificial intelligence has the potential to mitigate existing challenges FDA faces in conducting post-market surveillance for generic drugs, including insufficient data on bioequivalence compared to real-world effectiveness caused by underreporting of adverse events, high costs associated with undertaking large-scale studies to assess the real-world effectiveness and safety of generic drugs, and system limitations where reporting mechanisms that exist can be cumbersome or complex to use, as well as data security and concerns over data privacy of patient health information.

However, AI/ML has the potential to mitigate some of these challenges. For example, performing real-world data analyses of electronic health data to identify trends in adverse events, which can provide insight into the long-term safety of generic drugs, as well as training AI/ML tools on historical adverse events to predict the potential for long-term effects based on a drug's properties, patient factors, or other previously reported events, as well as providing comparative safety analysis of generic drugs and their potential effects.

When implementing such tools, the agency should carefully consider regulatory compliance, such as ensuring the tools meet good pharmacovigilance practices, as well as patient diversity concerns and whether the data from the adverse event reports includes demographic data that can inform whether observed adverse events are from a diverse, representative patient population or whether the adverse events are only generalizable to a patient population subset.

There are also ethical concerns - assessing whether the algorithms used are inadvertently inscrutable - as well as security concerns such as improper data sharing, cybersecurity risks, and data privacy. The agency should operate under FISMA High compliance and include zero-trust capabilities to minimize the impact of potential breaches and risks associated with the exfiltration of models.

AI/ML capabilities are also well-suited for streamlining the regulatory review process through learning from FDA data to identify potential quality risks and predict future compliance issues, enabling proactive or more nimble corrective actions and ensuring adherence to regulatory standards to enhance, for example, FDA CMC and REMS-related operations, as well as analyzing historical FDA approval data, including factors such as drug characteristics, submission attributes such as therapeutic area, regulatory pathway selection, and timeline to approval, to better predict the probability of approval, which could be useful to address challenges with CMC, REMS, and sourcing of critical APIs.

AI/ML also has the potential to improve the prediction accuracy of PBPK modeling, for example, by integrating data from various resources, including drug properties and excipient interactions into dissolution profiles to improve model accuracy for complex formulations or complex routes of administration.

It can also be beneficial through imputing missing data points or conducting neural network-based simulations using virtual populations and applying transfer learning techniques to adapt pre-trained models to specific data sets, and also predicting parameters using deep learning methods based on similar compounds or known correlations.

As FDA considers greater adoption and use of AI/ML, the agency should also require robust, transparent, as well as explainable AI models with clear audit trails through rigorous validation of AI-integrated PBPK models against experimental data in comparison with traditional modeling to demonstrate reliability and suitability for regulatory decision-making, as well as require applicant use of explainable models to minimize the black box syndrome and review results for model transparency, as well as prioritize model interpretability through clear quality model development practices and documentation while keeping in mind data privacy and patient confidentiality concerns.

The use of AI/ML can advance and modernize generic drug development to improve post-marketing surveillance by training AI/ML tools to use representative, diverse patient populations and promoting transparency, both within the agency and externally, in the implementation of these AI/ML tools to reduce bias and ethical concerns, as well as enhance the efficiency of regulatory review by developing standardized methodologies and protocols for using AI/ML in quantitative analyses and modeling approaches for regulatory review, as well as providing training and resources for FDA staff to deepen their proficiency and understanding in the use of AI/ML technologies, and also improve the accuracy of PBPK modeling by supporting research aimed at using these AI/ML tools for improving PBPK modeling for more efficient demonstration of bioequivalence for complex generics.

In totality, our recommendations underscore the importance of many of the agency's existing science and research priorities for generic drug development, primarily priority number 7 and number 8. In our recommendation, we underscore the continued importance of these priorities and would make the recommendation to make use of language in priority 7 with model-integrated evidence to include AI and ML explicitly to signal its commitment to the expansion of its use.

Thank you.

Moderator: Thank you, Sebastian. You actually have 2 minutes to address any burning questions form the panel members or the audience.

Question: When you're talking about using AI/ML for supporting PBPK model development, for example, what kind of sources of data do you think could be used to train those models?

Sebastian Melgar: I think it would have to be historical data to try to inform those models better.

Follow-up: But from where, I guess, is my question.

Sebastian Melgar: Great question. Could you repeat the question again, sorry?

Questioner: Where would the model training data come from? Since a lot of it's either privately held or doesn't exist in the first place.

Sebastian Melgar: In some cases, that would be a situation where perhaps the agency could advocate for greater authority to collect that type of data to remove the competitive nature of it.

Moderator: Thank you, Sebastian.

Our next speaker is Mr. Brian Eiden, who is vice president of global life sciences technological operations from Capgemini Group.

Brian Eiden (Capgemini Group): Thank you, everybody. Alright, excellent. I promise you I have no differential equations. Thank you to the panelists, both from FDA and from industry. It's a pleasure to be here. Thank you also to my colleagues, some of whom are here today, who helped me with this presentation.

Just a word about me: my name is Brian Eiden. I lead global life sciences technical operations practice for Capgemini Group. I'm a veteran naval officer with branded and generic pharma industry experience and served as global head of operational excellence for Mylan, now Viatris. I know Andrew, you're on the line as well. I think we overlapped by about two years. I was out there when we did the generic Advair build in Dublin.

My team and I at Mylan devoted a great deal of attention to ANDA filing process improvement, and that's part of what I'm going to base my discussion on today.

Enabled by FDA, which supported the growth of generic therapies while protecting innovator financial interests, the industry has dramatically improved over time. Key legal foundations, including GDUFA, are shown here. Continuous improvements have also been made over time via Drug Competition Action Plan, CDER's NextGen Portal, and many others.

What's amazing: nine in ten prescriptions in the US are currently filled as generics, and an estimated savings of $2.9 trillion has been realized over the last 10 years from generics and biosimilars.

Despite tremendous success, challenges remain. These include demonstrating bioequivalence, managing patent exclusivity issues, ensuring regulatory compliance, providing adequate resources, and sharing knowledge. These challenges continue to limit the number and scope of approvals as well as the overall presence of generics in the market. However, advanced technologies used with traditional process improvement hold great promise for overcoming these obstacles, providing breakthroughs to improve access, reduce cost, and decrease the number of drugs without generic equivalents.

How do we do this? Let's examine the ANDA process with a simplified view from selection to FDA decision with timeframes noted.

Now consider available levers that we could use to improve the process. We can collect and aggregate data, describe the situation, diagnose what happened, make predictions, prescribe solutions, even create content. All of this is enabled, as you can see on the right, by different branches of AI, such as robotic process automation, speech recognition, and others. The key idea is to apply the right mix of technology levers to improve the process by reducing waste and errors, allowing for smoother, quicker, and higher quality filings.

We target levers to improve the process, not to explore capabilities of the levers themselves.

Now I want to come to my research recommendation. Looking in light of known pain points - and I think many of those, if you're involved in ANDAs, you'll recognize and see yourself in them - we suggest partnering across industry and with FDA to develop and test an AI proof-of-concept solution for real-time ANDA submission risk assessment and mitigation for a targeted group of filings, most likely complex generic filings.

Pain points addressed by the solution include submission errors, preparation time, and resourcing. These are shown in blue, while additional pain points not addressed by this solution are shown in gray.

The solution itself would provide a user-friendly interface that would proactively signal missing submission elements and create a probability of success indicator. Let's call that POS. It would input missing or likely to reduce POS elements and potentially generate best practices. As an analogy, think about the way TurboTax manages your tax submission, flagging what's missing, calculating real-time return and audit probability. Call this "TurboANDA" - came up with that myself.

Technically, this requires several elements: a model of submission review notes, regulations, and numerical data. This is where the data would need to come from. AI training on all criteria, continuous data incorporation to prevent drift, and also a knowledge graph for tracking information and neural networks for identifying clusters and outliers. This would work in the model with multivariate analysis and loss functions to link POS (the outcome or Y, the effect) with potential causes.

The proof of concept would also require guardrails to keep recommendations within range of available information. Bottom line: we propose a short, targeted proof of concept in this way to

demonstrate feasibility, followed by a pilot launch for quick wins, most likely targeted at complex filings.

But what's required beyond proof of concept? Concepts and use cases are insufficient to realize the full potential of these technological solutions. A supporting operating model and several enablers are essential, including collaboration among FDA, industry, academia, and vendors.

An end-to-end cloud-based ANDA platform is crucial for integrating this kind of solution and necessary information and must be supported by cross-industry FDA data stewardship. After all, the effectiveness of this data model depends on the quality of the data it contains. Lastly, a cross-functional, agile use case factory is needed to produce and launch use cases at scale sustainably.

We've made significant progress in ANDA filings, evolving from simple process improvements to piloting advanced technologies. However, our journey is far from over. It is crucial now to focus on quantifying solution costs and estimating benefits. From there, we can scale and improve well beyond our current expectations. Thanks for your time. I've provided a couple of additional slides. I welcome your questions.

Moderator: Thank you. We actually have 3 minutes. Yes, Dr. Zhao.

Liang Zhao (FDA): It's a very intriguing presentation. I just want to make sure our understanding is correct. Are you talking about an AI agent to assist the applicant to address any questions?

Brian Eiden: It's a great question. Thank you. Coming from industry, I always put myself in industry shoes. This primarily is a tool used by the prospective filer. Imagine an interface that's fun and graphical and allows you some real-time information to know if your ANDA is going to be successful. Having been on the receiving end of submissions, I can tell you, despite a lot of the collaboration which is fantastic with industry - better than it ever has been between FDA and industry - there's still a bit of the unknown. It can be frustrating: is the day that I'm submitting now going to lead to a probability of success with my filing, or am I going to have another meeting or a redo? So it's giving you real-time information to try to head that off.

Liang Zhao: In terms of the form, are you talking about a user interface? Are you talking more like an agent that can provide customer service?

Brian Eiden: I hadn't thought about that second one. That's pretty good too. If you extend the TurboTax analogy, there's the "click to speak with representative" feature. I hadn't thought about that feature, but no, I was thinking about a graphical interface that would be passive with respect to FDA. But you could certainly link that with customer service functionality. That's a good idea.

Moderator:: I have a question for you. How do you think AI can address the unique challenges with some drug products that may require some types of data that's not common or usual in ANDAs?

Brian Eiden: That's a limitation. It's a great question. If the data isn't common, it's probably not in a large language model, and then it would be hard to integrate. But just to pick up on the idea of real-time adaptive trials that another speaker talked about - you can actually link that to this as well. So for more complex filings, that's probably a good example. In its day, it was a fairly

unique bioequivalence study. Nobody knew about that form of generic when it was being launched. But that's one, and then when the next one comes, it would need to learn over time. So I would say the choice of applicability of filings would need to be limited to those for which you know at least enough, and then you'd have to factor in the rest as you go.

Moderator: Thank you, Brian.

Our next talk will be delivered by Sandyha Polu and Anil Bhatta, who are contract managers from Deloitte Services.

Sandyha Polu and Anil Bhatta (Deloitte Service): Good afternoon, everyone. I'm Sandyha Polu, and this is my colleague, Anil Bhatta. I have a background in digital health and tech strategy, and Anil is a data scientist with a background in pharmacology. We're both in the government practice at Deloitte Consulting. Today we would like to propose that FDA consider taking an AI-driven approach to quality signal detection for generic drugs.

Post-market surveillance of generic drugs faces several challenges. Most of the manufacturing resides outside of the US, yet FDA inspection capacity is limited, particularly overseas. There have been instances of falsified manufacturer data, and adverse event reporting is voluntary by certain key stakeholders. Add to this that more than a thousand generics are recalled every year. Most of those are Class II, and we have seen spikes in Class I recalls over the past decades.

All of these challenges taken together require alternative approaches, tools, and data, including non-traditional sources of data to enhance post-market surveillance. Anil will now walk us through the technical aspects.

Thank you, Sandy. One of the research priorities outlined in the 2024 GDUFA research initiative is to expand the use of artificial intelligence and machine learning, especially as it pertains to FDA's assessment of scientific evidence and advice generation. To that end, we propose a solution for detecting quality signals for generic drugs, really by leveraging the power of artificial intelligence, especially in natural language processing and predictive modeling, to offer a near real-time surveillance type of solution to identifying quality signals for generic drugs.

In contrast to traditional monitoring systems which really rely, especially for FDA, on voluntary submissions by industry as well as the agency's own periodic review, we propose a near real-time approach where we want to proactively identify signals before they appear in recalls or communications by the agency. Our approach is divided into four different steps.

Step one is data curation, where we look to collect multimodal data from a variety of different data sources. Then we get into exploratory data analysis where we'll look to utilize some of the common statistical methods to really get a good understanding of the underlying data before we get into the NLP and modeling.

Step 3 is really where we want to leverage some of the latest and greatest NLP tools for signal identification. Primarily in this step, we're looking for some of the standard libraries like named entity recognition and some of the more fine-tuned clinical large language models to identify key signals that will pinpoint us towards underlying quality issues. For example, impurities in vials, or some of the packaging-related issues, or some of the lack of efficacy that could be demonstrated in a lot of these public forums can be picked up and then fed into our modeling process.

Then we get into Step 4, which is where we want to utilize some of these features that we are generating using NLP and large language models to really inform our modeling, where we look to utilize some of the anomaly detection algorithms or some of the other more classical machine learning algorithms to identify patterns which will lead us towards signal detection. We also propose to use human-in-the-loop interaction, and the reason for that is really to then iteratively go back and see what we missed in our initial model and then be able to iteratively improve as we move forward.

In the next slide, I'll walk you through our technical architecture. But before walking into this, I do want to point out that we've already successfully implemented this particular type of technology in our ongoing work with CDER, where we use NLP and machine learning to really identify some of the regulatory starting materials in our supply chain work to really identify some of the supply chain issues that can happen upstream before we actually get into the real issue.

At a very high level, we have a three-phase approach. Phase one being data mining. This is really where we look to collect data from multimodal data sources, both structured and unstructured, but also, from an FDA standpoint, both traditional and non-traditional data sources. So non-traditional data sources like social media, some of the legal proceedings documents, trends in search engines like Google and Bing, and so on. But also some of the traditional data sources like Form 483s that FDA publishes as well as insurance claims data and some of the more structured databases such as pharmacovigilance databases like FAERS and MedWatch.

Once we collect this multimodal data, then it feeds into our data aggregation pipeline, where, based on some of the common data elements, we look to aggregate those data, which is then going to feed into our next step, which is modeling. Within the modeling phase, we look to use some of the common NLP techniques such as sentiment analysis and clustering.

At a very high level, sentiment analysis - we look to analyze sentiment of your unstructured data. In this sense, we'll be looking at negative sentiments that track for a given drug over a period of time. All of the negative sentiments would basically be indicative of some of the potential underlying quality issues for those generic drugs.

Then those negatively tagged observations feed into our next phase, which is clustering. In clustering, we're looking to get some more granular understanding of what's actually going on underneath. We're really interested in understanding some of the temporal aspects of it - what are some of the sizes of these clusters? What are some of the characteristics of these clusters? How do they grow over time? Some of the temporal analysis as well.

Once we have all of these insights, then we get into our next phase, which is reporting, where we then look to provide insights to FDA that they can take action on. We look to do some more thematic categorization. What are some of these quality signal issues that we're seeing? Are they CMC violations, or are they just unknown safety or adverse reactions that could be indicative of underlying quality issues?

And then ultimately get to the reporting phase where the agency has the ability to then actually interact with the reporting system. This is a dashboard that's going to have some of the generative AI capabilities where you can actually do prompt engineering-based questions, and based on your questions, you can actually get analysis really catered to your needs.

Again, to conclude, we propose a near real-time solution for quality detection for generic drugs. With that, thank you for your time, and we'll take some questions.

Moderator: Thank you Sandyha and Anil. We actually only have 1 minute for a very quick question.

Question: Is it correct that you don't recommend looking at medical data directly in terms of the data mining category - medical data from EHRs, etc.? In your slide, you're mainly focused on derivative data like social media and all that. Is that correct?

Anil Bhatta: Correct, but medical data from EHRs can obviously be incorporated into our pipeline as well. There is a lot of narrative-based text in the EHR data that could be informative to our process as well. So yes, EHR data can also be included.

Sandyha Polu: Just to add on to that, most of the data sources we mentioned in the presentation are publicly available data sources, with the exception of maybe some data sources that would come from FDA.

Follow-up: Do you think the approach would be accurate enough just with the publicly available data sources? Do you think eventually you'll have to go into the EHR and the actual medical data?

Sandyha Polu: EHR data would obviously be very helpful to have if you have the right data partnerships set up. But we have seen instances - there was just a device recall, and there was like a two-month thread on Reddit actually of battery device issues. So there are examples of publicly available data being enough to indicate signals.

Moderator: Thank you, Sandy and Anil, for your presentation.

Our next presenter is Dr. Anthony Cristillo, and he is a partner of digital health at Guidehouse.

Anthony Cristillo (Guidehouse): Thank you very much. I'd like to thank the organizers for including me. I'm a partner at Guidehouse, and for those of you who don't know Guidehouse, we're a management consulting organization. We're about 17,000 people strong. We cover health, energy and sustainability, infrastructure, national security and defense, as well as financial services. But our health practice area or segment is the largest.

I'm a partner in the digital health area, so I'm a horizontal, which gives me this lovely flexibility of supporting both federal and commercial clients. This is across FDA, CDC, NIH, as well as commercial entities - pharma, biopharma, etc. - and it's in biologics, small molecule drugs, generics, and medical devices.

Before I go too far, I promise I did not steal Brian's notes before I got up here because you'll see a lot of similarities here, only I think I went a little bit too far because I think I took a couple of different perspectives to this. But I loved your talk.

We build systems, we build large systems, we build algorithms, and we develop these algorithms to solve biological problems, like many in the bioinformatics space, clinical informatics, health informatics.

We do this because many of us came from industry. We came from developing drugs, developing small molecule drugs, peptides, vaccines, generics, and medical devices. We saw what it took to go from concept to clinic or from bench to bedside, really.

As a result, we kind of factored this into our thinking of how can we help and what do we need to do, and where can we help, and what other information is needed?

Today's talk, I decided to take a very high-level perspective on how do we leverage AI, ML, and NLP, how do we leverage generative AI, now that we're starting to talk a little bit more about LLMs, FMs, and do this in three ways.

Number one, the regulatory review process. So, in other words, I package this, as you see from the agenda, leveraging generative AI for expedited and more efficient ANDA review.

The next part of it is AI-informed routing - drug complexity-driven routing. We've talked about this with FDA in other areas with CDER and CBER, where the - and I'll say this, regulatory reviewers have it tough. Oh my gosh! The amount of information they have to ingest, the amount of complexity they have to deal with. First, the review of many of these drugs - you almost want to help from an automation perspective in terms of getting the application to the right reviewer and do this in an RPA-like manner.

And then help them through that regulatory review process.

The final part is where Brian brilliantly jumped to the finish line and said, "Hey, we can not only help FDA, we can turn this around and help industry," so that, and in so doing, help FDA, because better quality submissions means reduced time for regulatory reviewers to go through the submissions, whether it be ANDAs in the case of generics or INDs, etc. Make sure that they have complete submissions that cover all the bases, and therefore greater or quicker time to licensure.

Let's just start off with the challenges. On the left-hand side, you see manual review of a large body of literature, including Phase 4 surveillance, real-world evidence, worldwide data of reference listed drug is time-consuming, not always complete. Detailed regulatory review of ANDAs to assess for gaps in missing information is time-consuming, could delay the review process. Manual routing of the application to the appropriate FDA reviewers can be time-consuming, also delay the process. And then finally, manual compliance checks by industry prior to submission may not identify all errors, omissions, thereby creating delays.

What's the solution here? Well, the solution could be leveraging large language models, retrieval augmented generation or RAG for expedited and more efficient review of the literature base for surveillance data, real-world evidence, real-world data, and identify gaps within the ANDA submission.

Another solution is leveraging AI/ML and NLP for drug complexity-driven routing of ANDAs to appropriate reviewers and to help drug companies develop higher quality ANDA submissions.

I thought I'd take a step back because I have been criticized over the last I can't tell you how many years of believing that everybody believes or understands everything I understand, that we all speak the same language.

So I thought I'd take a step back and let's just review some basic concepts.

Artificial intelligence: the ability of computers to imitate cognitive human functions such as learning and problem-solving. Through AI, a computer system uses math and logic to simulate the reasoning that people use to learn from new information and make decisions.

When we talk about machine learning, we're talking about a subset of AI when we teach computers to extract patterns from collected data and apply them to new tasks that they may not have completed before.

And then finally, natural language processing: a machine learning technology primarily concerned with giving computers the ability to interpret, manipulate, and comprehend human language.

Now the buzz all around digital is generative AI. My children, my daughters, keep talking about ChatGPT and Copilot. I've got colleagues asking, "How do we use Copilot more effectively, more efficiently, and with a greater understanding of what's real versus what's not real?"

Let's talk a little bit about generative AI. It refers to artificial intelligence that can generate new content, such as text, images, music, similar in style or content to a given input. And those little pictures on the bottom are actually one of my colleagues, Dr. Brian Jones, and those are the many faces of Dr. Brian Jones generated with generative AI.

When we talk about foundation models, we're going to dig into generative AI. Foundation models literally is what powers generative AI, and these are pre-trained on a vast amount of data to understand existing content and generate original content, whereas large language models, which we talk about all the time, which is a subset really of foundation models, are trained on trillions of words across natural language tasks.

And then the next stage is pre-training an LLM, which basically means training a model, this LLM, on a large corpus of text - billions of words, trillions of words - to help the model learn the structure of the language or grammar and facts. Examples: ChatGPT, Copilot.

And then we have fine-tuning of LLMs, where we take that pre-trained model and we further train it with at least one internal model parameter, perhaps for a specific context or case, thereby transforming a general-purpose base model into a specialized model for a particular use.

And then we hear a lot about RAG - retrieval augmented generation - where it's the process of optimizing the output of large language models so that it references an authoritative knowledge base outside of its training data sources before generating a response.

A while back, I did this in the context - and I apologize, I know this is generics, but I'm going to talk for a second on biologics - but for cell and gene-based therapies, the idea was using LLM and RAG to ask some fundamental questions about the challenges and recommendations associated with development, preclinical manufacturing, and clinical development of cell and gene-based therapies for different indications, including rare disorders.

I used LLMs and RAG in order to understand what industry, what the world thought about the challenges in developing cell and gene-based therapies. These are the types of tools one can ask with the right prompts.

So the prompts are the questions you ask. One of my colleagues asked me how difficult prompt engineering is, and I said one PhD is not enough. You almost need two or three PhDs.

At the same time, and I say that tongue in cheek, because the extraordinary thing about drawing on the last 25 years of your life in terms of experience in drug development and understanding it to be able to then ask questions almost in the way you would speak to a child in defining all the terms that you're using to try to extract out the information you want.

What I'm suggesting is that generative AI has the potential and opportunity to make a regulatory reviewer's life that much simpler, to then use prompt engineering to amass all of this knowledge as they are reviewing. So instead of them manually looking for all this information, amassing it, reading it, reviewing it, etc., sitting with a tool, a graphical user interface, perhaps it's voice-enabled. Right now let's pretend that it's just type the prompt.

But the idea would be then you would ask a question of your tool that is built on an LLM and a RAG that points to the right data sets. And there's a plethora of different data sources one can point to ask questions about the generic drug and ask questions about the generic drug versus the RLD and ask questions that amass the data over the last, I don't know, 15-20 years in terms of chemistry, in terms of pharmacokinetics, in terms of safety, in terms of perhaps things that we missed during the initial clinical trial that through real-world data, real-world evidence, Phase 4 surveillance we now know. But the reviewer needs to assess that as they are reviewing the ANDA application.

Moderator: Anthony, we are over time. Okay, so 20 seconds, thank you.

Anthony Cristillo: Any questions I will do. Thank you. Thank you.

Moderator: We have Sarah Ferko and Ally Lu, who are managing senior consultants in artificial intelligence and analytics at IBM Consulting.

Sarah Ferko and Ally Lu (IBM Consulting): Hi, everyone. Good afternoon. My name's Sarah, and I've been with IBM for almost 10 years and working at FDA for over 7 years through IBM. My colleague Ali here has been at FDA for several years as well.

All right. So we're addressing research initiative number 8, expanding the use of AI and machine learning tools.

Specifically on this slide, we just want to essentially cover that IBM provides AI, data, and cloud solutions. We've been supporting FDA for over 15 years across multiple concurrent task orders. We support CDER, CBER, CFSAN, and ORA.

All right. So essentially, what we want to do here is talk about generative AI and its usefulness within the generic drug review.

Specifically, the four functionalities of GenAI we want to talk about are summarization, semantic search with question and answer capabilities, content creation, and code creation and conversion.

What we want to do is talk about these and how they can benefit the OGD reviewer when they're looking at ANDA submissions.

So, starting with summarization, GenAI can be used to extract, summarize, and compare data. Within OGD, one interest area would be to extract unstructured text from the ANDA submission. We know that a good amount of the submission can be in unstructured PDF, so essentially extracting that data and summarizing it more effectively.

Taking that one step further, combining the extracted summarized text with structured text or structured data that's also extracted from data sets and other sources to create what we're calling application-level reports for the ANDA submission. The utility of this would be that this would essentially be an aid for the OGD reviewer to kind of cover key attributes that are decided upon through requirements gathering with OGD reviewers.

Taking that one step further, thinking about a comparison report, where we also extract data from the NME or the original NDA/BLA submission to then compare with the ANDA submission. And again, this would be based on attributes that are determined useful from OGD, and we work together to collect those requirements.

Semantic search with question and answer capabilities. So in this area, supporting the OGD review, we know that, like I mentioned before, a lot of PDF can come in with the submission. And when you think about how big the eCTD is, with all the various sequence folders, one submission can actually be comprised of many folders with much unstructured data. So thinking of essentially using a chatbot here to support information retrieval by letting the GenAI tool ingest all the data.

And then the OGD reviewer being able to quickly ask questions, and then the tool providing the answer, but not just the answer, but also the source where it came from. So this protocol document, this CSR document, wherever that information came from, so that the reviewer can go right back to the source. Not just see the answer, but know where it came from to provide that traceability.

The third area is around content creation. So, GenAI can be used to support critical tasks during the ANDA submission. So one area around content creation can be drafting IR language. This is one example we came up with. But ultimately will help reduce the time between creating and sending that IR, and ultimately reducing any gaps in the review timeline. And for this one, large language models can be used to generate suggested data based on previously submitted IRs.

And the last one with code creation and conversion. The last idea we want to talk about today is just acknowledging how useful GenAI is when enhancing developer productivity for system development, enhancement, and maintenance. So when you think about review tools that OGD is using such as the BEAM tool and other tools, the developers can use GenAI to help them code enhancements for those tools, as well as the programmer themselves when they're reviewing the data. Like, if you're looking at PK data and you want to run an exploratory analysis, GenAI can generate snippets of code or little sections or entire programs. It's really good at optimization as well as identifying bugs and vulnerabilities in code, so can be used as a helpful tool for the OGD reviewer themselves.

Alright, and just to keep it within the 5-minute timeline, I just want to close by mentioning that IBM's been implementing similar solutions within FDA and across different agencies, and we would love to talk more if of interest. So thank you for letting us present today.

Moderator: Thank you, Sarah and Ally. I believe we have 1 or 2 minutes at most to take a question

Robert Lionberger (FDA): Your talk was very product-focused. So I want to get at what the research questions are. So what are the things in your talk that you're not able to do with current technology where you need research and development to make these things more effective for the generic review process?

Sarah Ferko: So we were looking within research priority area number 8, which a portion of the GDUFA priority areas were focused on enhancing the generic drug assessment. And so we were just coming up with ways that we could directly support OGD and the reviewers themselves in their assessment.

Clare Butler: Just one quick question for myself. What potential disadvantages would such a paradigm have for a potential ANDA submitter?

Ally Lu: Well, so I think it will improve the efficiency of the review process, right, in allowing the whole community to expedite the timeline for the generic drug development and approval, and then for the industry itself, the sooner FDA will be able to provide feedback to the companies, the faster the companies will be able to address the feedback from FDA. And that way, it will also be economically more efficient for the industry. If that makes sense.

Clare Butler: Yeah, no, it makes sense. And is there existing data that would support this?

Ally Lu: Yeah, so we have done similar work in other parts of FDA with new drugs and other centers, and we can help OGD to identify some sample applications to conduct proof of concept pilots, if you will. So we have the expertise in this area.

Clare Butler: And in terms of, say, human error risk assessments? Would that all be included?

Ally Lu: Yes, right?

Moderator: There is more time. We can discuss this during the panel discussion,

Ally Lu: we will be very interested in continuing this discussion with you.

Moderator: Thank you for all the speakers.

So we can take a short 5-minute coffee break and refresh ourselves, and then we'll be back to the same seats. Thank you.

Let's start our second session of public comments. We are going to start with Dr. Ashlee Brunaugh, and Ashlee is a systems professor from pharmaceutical sciences at University of Michigan.

Ashlee Brunaugh (University of Michigan): Okay, thank you for the opportunity to speak today.

So today, I'm going to be essentially pitching the idea that mucus is really important in understanding and modeling the impact and predicting inhaled drug bioavailability.

I just want to bring attention first off to this issue of actually developing generic dry powder inhalers in particular. So we're in a situation where a lot of these products are past their

exclusivity period and perhaps have been for a while, but still have not - we don't have very many generic products on the market, and a lot of this can be related to this issue of requiring clinical endpoint studies to demonstrate bioequivalence.

So ultimately, this makes the development of generic DPIs a very risky and high-cost endeavor.

Currently, the in vitro gold standard for understanding the performance of dry powder inhalers is called cascade impaction. So cascade impaction can provide information about the aerosol particle size distribution as a function of the device and inhalation parameters. And it can give us some idea about the potential location of where that drug particle may deposit in the lung.

However, a big gap with the current in vitro methods is that there's really no information provided about how that particle is going to behave after it's deposited in the airways.

Whenever we're thinking about bioavailability, particularly local bioavailability, we really need to understand this post-deposition phenomenon in order to predict the drug concentrations at the site of action.

So ultimately, if we're talking about an inhaled drug particle, the dissolution and diffusion rates must exceed the different physiological clearance rates present. So mucociliary clearance and macrophage phagocytosis, in order for that inhaled drug to reach its target in the airway epithelia.

So the interaction between these inhaled particles and the lung lining fluid is going to be impacted by their product attributes. So these can include surface properties, particle size. And it's really important to understand these interactions. But there currently exists no standardized fluid to assess and predict how that particle is going to interact with the lung lining fluids. And this is in contrast to other delivery routes, such as oral drug delivery.

One of the areas that my lab focuses on in particular is these mucus-drug interactions that can take place. So the reason why we're so interested in mucus is because it's really been designed by evolution. It's an important component of the innate immune system to block these exogenous inhaled substances from reaching our airway epithelium.

So mucus can filter inhaled substances on the basis of size as well as interactions, so it can filter out hydrophobic or charged drug particles and molecules. And ultimately, this can result in a slowing of the diffusion rate.

And again, these interactions are going to depend upon the properties of the drug products. But it's also going to depend upon the properties of the mucus, and that can vary as a function of location in the lungs as well as the disease state of the patient.

So why are we interested in mucus compared to other lung lining fluids? So if we're thinking about lungs and the peripheral airways, you have a very thin diffusional barrier, large surface area, extensive blood flow, and the smallest particles are going to be deposited in these regions.

So really, not quite as concerned about dissolution in this more peripheral air space. But if we're thinking about the conducting airways where we do have receptors for these different drugs that we deliver via inhalation, you have this, you know, potentially quite thick mucus layer. And you're going to have bioavailability and kinetics that are controlled by innate properties of the molecule, properties of the drug particle, and how fast that dissolution and diffusion can occur.

So this is kind of my dream or pitch, I guess. So currently, what exists is we have these in vitro cascade impactions. More and more, we're developing these computational fluid dynamic approaches so that can give us a good prediction about regional deposition data in the lungs.

So the way that we could enhance this is first off creating improved and validated artificial mucus models that differentiate between disease and healthy mucus, but also encompass how age, sex, and environmental influences can impact airway mucus composition.

And then the second major area of focus is to understand how these particle surface properties can impact these wetting and immersion behaviors. Ultimately, this could identify critical quality attributes for DPIs and support the development of Q1/Q2 sameness approaches.

So the desired outcome for these studies would be improved efficiency of generic drug product development. For novel drug products, we could have a reduced risk moving from this preclinical to clinical translation stages, and then potentially, you know, depending upon the insights that we gain from understanding this mucus composition and its effects on inhaled drug bioavailability, we could develop personalized dose strategies and product selections depending upon the disease state and severity of the patient.

So that's it. Happy to answer any questions. Thank you.

Question: Thanks for the presentation. Just wanted to ask, do you have any data which discriminates between two formulations, say, which behave the same in NGI or ACI, but due to different mucus interactions, there could be a difference in the bioavailability?

Ashlee Brunaugh: Yeah, that's one of the areas that we're working towards right now. So first, just trying to understand from a molecular standpoint what FDA-approved molecules interact with the mucus and then adding onto that to incorporate drug product properties. So understanding, perhaps, how changes in surface energy can impact it, changes in hydrophobicity, for example, the use of magnesium stearate. But that's exactly what we're interested in.

Moderator: Thank you, Ashlee.

So we can go to Dr. Jinxiang Xi, and he is associate professor of biomedical engineering at University of Massachusetts Lowell.

Jinxiang Xi (University of Massachusetts): Thank you for the opportunity. Today I try to talk about the possibility of how can we use AI and apply it into computational fluid dynamics? I try to give some details, and also here the purpose is we try to develop an interface so that is for industry, for FDA. You can use that to try to study for different drug conditions.

And all this model should be validated, easy to use, and it can be explainable. So we have this. I will concentrate on these three emphases.

So here I try to talk about what CFD is. Whenever, for example, I have a DPI or an inhaler, so what happened? So anyway, that is what we try to do. First is we need to consider three conditions: the airway geometry, the boundary condition, and that is the computational mesh. So first of all, we get the data, we build the airway. And the geometry basically is a quite big issue for CFD, reflecting what I have done in the past 20 years.

As a CFD engineer, I found that I basically only do four things. The first thing is, I build a geometry, basically from CT/MRI, and the second is, I deal with dynamic boundary conditions, and the third one is, I try to include different physics, not including the fluid mechanics, but heat transfer, evaporation, condensation, moisture that can happen when, like, we inhale a drug. And the last part is, I found that many times I spent time studying different factors, for example, for particle different particle size, velocity. So this process is very complex. It consumed me 20 years.

And here what I try to do is, is it possible that I can wrap it, and so that I can bring an interface to the industry, to the FDA. You can use that, not as a black box, but you can have some options to study for different patient groups, to study for different devices, and also this model can be adaptive, so that once you have more data, we can use that to improve our model. So here I try. Let's see the four emphases. I try to talk, and if, because this one does not have a laser, I cannot point to that. So first one, what I try to talk about is geometry, and I do not want a formal origin or airway. Whenever we deliver a drug, we cannot neglect that. That's consumed part of my career.

And so how, for example, we can consider different patient groups, and either it is the male or female, or different ages, or do we either healthy or diseased, or for diseases, for different stages.

Is there any good way or better way we can to generate that? Not, for example, as me right now try to do it, spend months, try to get the geometry and mesh it, but try to use a test more like just give the information and generate the geometry. Is that possible? That's the absolute question. I will show that it is possible.

The second part I try to talk about is the variability, because for the drug, there's so many, many variability, not including the geometry, the different the population, but also from the drug, the formulation, the particle size, the flow speed when we try to do the drug delivery, the strategy for different habits. Right? So all these different is variability. The third part I try to emphasize

the third part basically is the information as CFD. I think anyone who knows CFD here, you know that it would generate pounds of data 3D flow particle. You do not want so many details, but you want to know the reason behind it.

And how can we find? How can we explain the data with a very clear explanatory, and that is, I try to do that also. I have some answer today, some suggestion, maybe called the last one is called validation.

Our model, our CFD model, especially AI-based. One cannot be a black box. You cannot explain. You need, for example, to make sure it is correct. I will try to talk about one method that is, use the experiment method and try to validate not only, for example, it is basically called compressed sensing used very few experimental data. Try to get very good results. Google, to be true. Right? I will be a multitude.

So yeah, I will go through that. So basically, here is the interface, the user input, the user input can be either the target, your patient group, your devices, formulation and your delivery protocol, and what you will then get is you can get biological equivalence, dose variability, uncertainty, something like that.

So the first one is, I try to concentrate on the patient group. How can you focus the traditional way if you try to build a patient-specific get the CT data. And MRI data use software like 3D Slicer or MIMICS. Try to do the 3D geometry you. That is the STL file, very difficult to do that. And here is a method I have used in 2021 is called the shape modeling.

I feel that this is the data science applied. Not AI here, but it is a data science. We try to learn from different models, and we can generate infinite number of geometry very easily, or I can do that. This is a very that's an excellent example. Suppose that here I give you 11 nasal models. I only concentrate on the nose.

I generally extract some information about the feature of the nose, and use the major feature to generate any kind of nose. Yes, it can. It is called the principal component analysis PCA.

Once we get this mean feature, we just use linear equation and they will get they will give you a model, and you change your tweak the coefficient, and they will tweak the feature of the model. And basically, this one is very magical. The first model. The first component will be how big your nose will be. The second one will be how tip it be so for different component or different feature or age, innovative or age, and they represent something. Now I want to let you to translate to the lung, to the airway, to the oral cavity or nasal cavity.

So this feature, basically, if we have a group of patient-specific data and use this statistical modeling, and we can generate, we can find the main feature and generate infinite number of new geometry.

And here, of course, is the basic shape is my main method, it is better to use is the statistical model. So here is one example I use for the lung, and I only try to study the left lobe.

So I use this statistical modeling only to change that part before that. Usually it is very difficult to achieve this.

The second one is also related with geometry, but try to study the sensitivity. And here is called the adjoint analysis. So this is the variability. You can consider variability, error. So the elementary flow. And we can develop the model. The here is the third one, the explain, explain how you explain your data.

We use AI, but we try to concentrate on informatics. Flow informatics, which is not only the detail, but to try to get the big structure because time limited. I didn't have time to do that. The last one is validation, and it actually is a compressed sensing compressed. The sensing, which is basically only become popular from 2004, when, if you familiar in UCI.

There is the almost the Mediterranean, Larry Stoll, so him proved that it is true we can use it to validate our model and use very few validation. Thank you for your time. Sorry for the overtime.

Moderator: Thank you, Dr. Xi.

For the sake of time, we can move to Dr. Guilherme Garcia, and Dr. Garcia is assistant professor at Marquette University and the Medical College of Wisconsin.

Guilherme Garcia (Marquette University and the Medical College of Wisconsin): Thank you for the opportunity to give this five-minute presentation.

As you know, few generic metered dose inhalers have been approved by FDA. Pharmaceutical companies are currently developing new generation MDIs that use green propellants to reduce global warming.

In FDA's weight of evidence approach, computational models can be used as evidence to demonstrate the bioequivalence of a candidate generic MDI to a reference product.

However, gold standard computational methods to evaluate the bioequivalence of MDIs have not been established yet, especially in the context of green propellants.

Well, FDA has recognized the need for more research in this field. In the fiscal year 24 GDUFA science and research priorities document, it states that one of the priority areas is developing efficient approaches to support transitions by generic products to utilize more environmentally friendly propellants.

But there are many challenges and open questions. So one potential study design to validate methods for testing the bioequivalence of MDIs is to fabricate MDIs with the new green propellants and compare their performance to the commercial MDIs that use the currently used propellants.

We can then perform in vitro testing to compare how replacing the propellant affects the plume geometry, spray velocity, particle size distribution, and other characteristics.

And we can then perform in vitro experiments to quantify the regional deposition of the MDI in airway replicas that have multiple regions and then use that in vitro data to validate CFD methods to predict the regional doses and then using the regional doses as input to PBPK models, estimate the bioavailability and the PBPK models can be validated with the drug concentration in the blood of human patients available from the literature. In the next three slides, I'm going to highlight three areas that have to do with validating the CFD simulations from in vitro experiments and the challenges involved there.

So the first area that I think needs more research is this issue of particle bounce. So studies have shown that particle bounce can affect the particle size distribution determined by cascade impactors.

And there's growing evidence in the literature that particle bounce can also affect the regional doses in airway replicas. So our group with collaborators recently completed this study in which we compared CFD estimates of the dose of nasal sprays that deposit beyond the nasal valve and reach the posterior nose, which is this area highlighted in green in the model. So these models had an anterior nose that is purple and a posterior nose that is green.

So the CFD simulations predicted that only 24% of the dose reached the posterior nose on average in the 12 unilateral nasal cavities, while the gamma scintigraphy experiments measured that 46% of the dose reached the posterior nose.

So we performed a very extensive parameter sensitivity analysis to investigate how many parameters like spray velocity, spray cone angle, particle size distribution, and other parameters affected the drug distribution, and none of them were able to explain this discrepancy.

So we concluded that the most likely explanation is the assumption in the CFD simulations that the particles deposited at the first position where they hit the wall, the trap boundary condition.

So I think there's a need to validate wall film boundary conditions for CFD simulations of pharmaceutical aerosols.

Another area that I think needs further research regarding MDIs and taking into account the different evaporation rates of different propellants is the effect of air humidity. So MDIs are often characterized in laboratory conditions with room air that's dry air, while inhaled air is quickly humidified to 100% relative humidity in the respiratory tract.

So this paper by Wan et al. 2024 reported that the relative humidity had a significant impact on the dose of MDIs that deposit in the USP induction port. So up to a 20% difference in throat deposition - 20% of the metered dose, which was a significant impact.

So there's a need to develop CFD methods to estimate the impact of air humidity on regional doses delivered by MDIs.

And then the last area that I think needs more research is regarding electric charges. So this paper by Karabetova et al. 2019 compared the dose of MDIs in metal versus polymer mouth-throat models.

And they reported that the fluticasone propionate had a higher deposition in the polymer mouth-throat model - about 14% higher in the polymer model. And the two airway replicas had the same geometry. They were just fabricated with different materials.

So I think there's a need for more research to develop computational methods to understand how electric charges affect the regional doses of MDIs in airway models. Thank you very much.

Moderator: Thank you Dr. Garcia, I think we have 1 minute for one question from the panel.

Question: Hi, this is Bryan Newman. Good presentation. So I particularly like the comments on the electric charge, and I know that dealing with the different propellants, there's been some research to show that certainly that can affect the charge of the droplets. So wondering if are you purely just talking about the charge on the surface of the say, mouth-throat, are you talking more about the actual charges of the droplets?

Guilherme Garcia: So I actually not actively working on this area. So this is a collaboration with Dr. Andrew Martin at the University of Alberta. And this is an observation that he has from his own lab that MDIs generate electric charges, and when you measure the deposition in plastic versus metal models, you have different results.

So that's a challenge for CFD modelers like myself. Because if you don't account for that, and you're not aware of it, you can have these significant discrepancies between the CFD simulations and the experimental results. And you don't know what's going on, right? So I'm just highlighting that I think this is one area that needs more research.

Moderator: Thank you, Dr. Garcia.

We can move to Dr. Darragh Murnane, and Dr. Murnane is a professor of pharmaceutics at University of Hertfordshire.

Darragh Murnane (University of Hertfordshire): Great. Thank you very much. So I'm going to have a bit of a different slant here, which is how we can use analytical techniques to help improve predictive models of performance as well as build in silico models for digital twinning.

And the approach we take is to use X-ray computer tomography. So the types of products that we're interested in here are particularly products that involve micronized drug particles as well as low dose products, which we know are very challenging to achieve bioequivalence and when developing a generic equivalent. So really, we're looking at powders and capsules, we're looking at tablets, and we're looking at dry powder inhalers here.

So we use micronized APIs because they're essential for delivering drugs to the lungs. But they're also used because they're highly beneficial for poorly soluble APIs. So we're not going to get away from using micronized particles.

Reproducibly manufacturing these products is actually quite technically challenging. So there's often segregation within the blends. And then there's also physical instability issues which need to be taken into account.

And the real big problem here, when it comes to bioequivalence, is around content uniformity challenges. So if we've got content uniformity issues, it's going to be difficult to show bioequivalence during your ANDA application.

So our question here is, how can imaging science contribute to predicting product performance?

Really, when we look at dry powder inhalers as an exemplar of low dose, micronized products blending, there's been some excellent progress in modeling sciences to try and understand, after the generation of the aerosol from the DPI, around what the structure of that aerosol is post-actuation, how that's transited through the airways, and also then through deposition, dissolution, and absorption modeling.

Really, if we look at the pre-actuation step, most of those models are highly idealized at the moment, and the questions that we're trying to address are whether there's a better way to understand that pre-actuation formulation. So asking ourselves some questions: are there meaningful links between the structure of the powder pre-actuation and the drug delivery performance?

How does manufacturing and change - even small, subtle changes and minor changes in manufacturing - affect the pre-actuated structure as well? And is there a sampling method that can maintain the agglomerated state of the bulk powder? So can we characterize the structure in the bulk powder?

Now, the challenge here for X-ray computer tomography isn't just around image analysis. It's actually, how do we generate that image in the first place? So there's a key challenge around the length scales. When we're looking at these products, we need to be modeling both on the nanometer as well as the millimeter scale.

And that's a real challenge. So if we look at the standard XCT image analysis at the moment, you can see that an image like this that's taken with a standard laboratory instrument lacks the resolution to see and image micronized drug particles within this blend. And even if we go up to synchrotron instruments, so the more advanced instrumentation, actually, the imaging is very noisy, and actually makes it extremely difficult to identify and pick out micronized drug particles.

So we use an approach where we combine nanoscale CT with micro CT imaging. And you can see an example in this image here, where we can see the individual drug micronized particles stuck on the surface of a carrier particle in an agglomerate. So our approach is actually able to achieve that resolution of particles to study what's going on at the nanoscale resolution in a millimeter-scale sample.

And what can we do with this? Well, if we start to use this technique to probe across multiple length scales, you can see that we're able to characterize the powder microstructures within that bulk powder. Be that in a capsule or in a blister, and we can see two examples here of a drug that has very poor content uniformity within that blend sample. There's an agglomeration of the drug that causes it to aggregate within the blend versus another drug here in green, where we see very good homogeneous distribution of that drug throughout the powder blend.

So what are the kind of problems that we can solve with this during generic development challenges? Well, really, the key question that we're addressing here is the formulation and device similarity, and the in vitro test equivalence. Looking particularly at that Q1/Q2 microstructure equivalence.

And the key benefit about this X-ray micro CT is that it's a non-destructive Q1/Q2 microstructural assessment. We can image inside blisters. We can image inside capsules. We can image inside tablets.

So it's a non-destructive approach. And if we look at the types of things that we can generate during the image analysis, we can pull apart fingerprints. So microstructural fingerprints that are specific to the drugs. We can see in the top row here is one drug - fluticasone propionate - and the bottom row, it's a second drug - budesonide. We can see we get very different fingerprints for these two drugs.

And also depending on the formulation structure. So we've got different ratios of drug to fine lactose as we go from left to right here. So we get these specific fingerprints.

What's quite interesting for us is that there's an intra-sample heterogeneity. So even in a sample that passes content uniformity, we can see in different regions of that sample. So from top, middle to bottom that there's differences in those fingerprint structures as well.

We can also use this analysis to de-risk material supplies. You can see here a nanoscale resolution of carrier lactose, and we can see within that commercial lactose, these cracks that exist within the crystalline structure that can't be seen using any other technique.

So this doesn't exist in every batch of lactose that we receive. So can we use these X-ray CT techniques to understand sources of product failure, but also to identify unknown sources of batch-to-batch variability? And can we use that as a predictive way to de-risk supply chains?

So finally, to finish up with some questions, then. So there are the techniques and the capabilities that we've got. Some of the questions that we raise around knowledge and understanding of the products are, does that bulk microstructure correlate to the aerosol microstructure after it's formed? So is research needed to address that? Will bulk microstructure equivalence equate to bioequivalence?

And can we use bulk microstructure to build predictive digital twins to understand how these products are going to behave throughout SUPAC changes?

And then with technical questions, what are the limits of detection for different APIs and blend types? How do different API chemistries affect the limit of detection for this technique? And what is the appropriate scale of scrutiny for assessment?

Moderator: Thank you. We have 1 minute for a question from the panel.

Bryan Newman (FDA): Thanks for the presentation as well. So for this, I guess the first part kind of gets to the main area. So the idea of the pre-actuation characterization and relation to the aerosol performance. So I'm wondering, has your group actually looked at the differences of performance using this technique with the different products just to get like a sense of where this is trending for that?

Darragh Murnane: So we've looked at aerosolization performance for these two particular substances as well. We've identified differences with them. We're currently working with some partners with in vitro impaction data using a whole variety of different impaction data as well, so we are working, looking at that at the moment. But what I say is that there's clearly a need for deeper research to make that link, Brian. And I think that's where the research question lies.

For this to be a technique that can be adopted by the industry, we need to identify what that equivalence test is. But I think there's another clear point which is around the pharmaceutical quality side. It's not just about the predictive sciences, although that's this session. It's also whether we can use it to predict product failures and quality issues, not just the in vivo performance. And I think that's just as important in terms of the quality of the medicine and an ANDA filing and getting through SUPAC changes. That's also a key part. If we can start to clean out the need to use PK studies and SUPAC studies, that would be a massive advantage for the industry as well.

Moderator: Thank you, Dr. Murnane.

So we can go to our last speaker from the in-person talks, Dr. Jeff Schroeter, and he is a senior scientist at Applied Research Associates.

Jeff Schroeter (Applied Research Associates): Hi, thank you. Good afternoon, everyone. Jeff Schroeder. I'm a lead computational modeling and respiratory dosimetry group at Applied Research Associates. So we primarily focus on development of modeling and simulation tools and regularly collaborate with universities and labs to also support other approaches to further enhance and develop those models mainly for bioequivalence review and other applications within regulatory agencies.

Of course, we're here to discuss predictive tools for generic product assessment. We, as with others that have presented today, promote and encourage the use of modeling and simulation. I'm not necessarily advocating for, you know, in vitro experiments and other approaches other lab approaches directly informed by equivalence, but more to support model validation. That's where we're coming from. So I'd like to specifically talk about a couple of areas that we have interest in supporting our model development. This is going to focus on nasal spray products. But a lot of it can probably be extended to orally inhaled drug products as well.

So for nasal spray products, modeling and simulation tools have primarily focused on two areas: that is the computational fluid dynamics models of the deposition and PBPK models of absorption and bioavailability, both of which you've heard about some today. From a drug delivery perspective for nasal sprays, the problem is maybe a little simpler than orally inhaled products, simply because the droplets are only traveling a few centimeters.

However, one repercussion of that is that device parameters and other use parameters can greatly affect deposition, and so using modeling approaches to kind of inform how these effects propagate through and can affect bioequivalence is something of concern.

So our team has some project experience on both sides of this. We've collaborated with Dr. Garcia from Medical College of Wisconsin, and others at UNC Chapel Hill to develop CFD models of nasal sprays. We're certainly not the only ones. There have been a number of other labs who have developed CFD models of nasal sprays along with labs that have developed in vitro approaches for measuring deposition.

And I think all these studies have been fabulous, and they help inform, help complement each other. And I think one area of research is that these, some of these results, rather than treating them on an individual basis need to be brought together. So how can we do that? And we'll talk about a little bit about that on the next slide.

Another approach is on PBPK modeling. Again, we've developed some models for corticosteroids specifically. There are PBPK models for a number of drugs, nasal or otherwise.

And PBPK models typically rely on some sort of parameter fitting or model fitting to data or parameter estimation, I should have said, and ultimately sensitivity analysis, and uncertain sources of uncertainty have to be identified. And so then, as a result of that, experimental studies can be identified to help support those parameters, to reduce that uncertainty.

So solutions, as far as we see it, are the use of machine learning models. Specifically, one area is looking at nasal spray deposition. As I mentioned, the use parameters and device parameters can greatly affect deposition. There's been a number of CFD studies that have shown this. Again, if we have a number of papers that have shown various aspects of this.

However, to be able to bring all this together, we think ML approaches can greatly enhance that. So looking at ML approaches to see how critical quality attributes, such as spray velocity, or droplet size distribution can affect regional and total deposition.

And of course, machine learning models are very data intensive, so there could be a need for additional CFD studies to fill in these gaps.

Specifically with PBPK modeling, one thing that we've seen is that permeation through the nasal epithelial layer greatly affects systemic concentrations. It's very sensitive. Most models rely on estimates of diffusion and permeability. This is an area where model validation would greatly benefit these modeling approaches.

And finally, Dr. Xi touched on this as well is the idea of these unified software platforms so that we can go end to end. CFD models are very informative in one sense. PBPK in another sense, incorporating ML models into that brings up another perspective. So if we can have unified software platforms so we can get end-to-end predictions from device parameters and usage parameters down to both local concentrations and systemic concentrations. I think those can be

used to develop tools that anyone can use on a regular and easy basis for doing these types of analyses.

So. Thank you.

Moderator: Thank you, Jeff, so I believe we have time to take two questions.

Moderator: If not, we will discuss in the panel presentation. Thank you, Jeff, so now we will move to the last batch of virtual presentations, and our first presenter is Dr. Guenther Hochhaus, who is a professor from University of Florida.

Guenther Hochhaus (University of Florida): My name is Guenther Hochhaus. I'm a faculty member at the University of Florida, and as a disclosure, my lab has received correspondence, research contracts, and grants mainly in the area of bioequivalence assessment of inhalation products.

As most of you will know, FDA applies the weight of evidence approach for inhalation drugs. The reason for this approach was that blood is downstream of the lung or the nose, that FDA felt that standard PK studies cannot assess bioequivalence at the site of action.

Thus, within the weight of evidence approach, in vitro studies, pharmacokinetic studies, and clinical endpoint studies have been suggested. Within this approach, mainly the clinical endpoint studies present a big challenge.

Therefore, FDA has initiated programs that evaluate alternatives to the clinical endpoint studies as a means to determine the lung dose, drug residence time, and regional deposition. Those are three factors that are very important for the bioequivalence of inhalation drugs.

These approaches that have been developed include tools to assess the regional deposition for inhalation products, the use of anatomical mouth-throat models in conjunction with typical inhalation profiles have been evaluated. Computational fluid dynamics for predicting regional deposition of inhalation drugs have been developed.

Approaches to assess post-deposition events, for example, dissolution tests or MDRS methodologies for nasal sprays have been used.

And also methods to assess deposition and post-deposition events together, like pharmacokinetic modeling through population pharmacokinetics or through physiologically based pharmacokinetics have been characterized.

As a result of these GDUFA activities, alternative approaches have found their way into very recent product-specific guidances, for example, for formoterol like Aerospan, which allows the pathway without clinical endpoint studies.

Assessments include standard evidence, particle size distribution experiments, spray pattern, but consequently use of realistic mouth-throat models, PK studies with and without charcoal.

There is, however, a caveat to it, as FDA suggested, that optional computational modeling studies may be used to establish bio-relevant limits to differentiate between different products and to assess virtual bioequivalence studies.

Validation of these computational methods is not trivial. They include comparison between predictions and data from in vivo and/or in vitro sources for reference standard, and at least one other product that differs from the reference standard, individual deposition, systemic decay or lung tissue PK.

Such studies, for example, might include scintigraphy studies and might have to integrate anatomical and physiological conditions across the patient population, and their availability.

In short, development and validation of such methodologies, computational fluid dynamics, PBPK, and virtual bioequivalence studies is not trivial, and time and resource consuming, potentially resulting in companies using the traditional weight of evidence approach, especially as risks and timelines are clearly predictable.

I would like to propose the following research activities to further streamline bioequivalence assessments for inhalation drugs.

These activities would consist of first developing and validating computational methods, CFD, PBPK and PopPK for a wide range of model drugs covering the design space as it relates to device, formulation, and physicochemical properties of commonly used APIs.

Second, use these models to link differences in the in vivo and in silico performance. The projected differences observed in bio-relevant in vitro and standard PK studies.

Such studies might include realistic APSD experiments, lung dose predictions in reproduction, behavior and standard PK assessments, and then you see.

Third, based on this comparison, define generally applicable bio-relevant limits for specific in vitro and PK studies.

So the final goal of these proposed studies is to allow use of standard in vitro PK approaches within the bioequivalence assessments of specific products without the need for applying computational methods. I believe that would help further streamline and facilitate the development of generic inhalation products.

With this I would like to close. I would thank you for your attention and FDA for allowing me to provide these short comments.

Moderator: Our next speaker is Dr. Yu Feng, who is associate professor from School of Chemical Engineering, from Oklahoma State University.

Yu Feng (Oklahoma State University): Hello! My name is Yu Feng. I am an associate professor in school of Chemical Engineering, Oklahoma State University. I am also the academic co-chair of pharmaceutical strategy task force in AIChE.

Representing the two parties together, I am happy to share our vision on the benefits of CFD-PBPK models, together with machine learning and deep learning on accelerating inhalation innovation and improving regulatory science.

The reason we think the CFD-PBPK model as well as AI technology can help in accelerating inhalation innovation and improve regulatory science are as follows.

First, while we talk about CFD-PBPK models, we always compare its capability against PBPK-only models.

So when we employ the computational fluid particle dynamics model, we always employ the subject-specific 3D physiologically related human airway geometry for predicting the transport and deposition of inhaled medications.

So by using this kind of model, we are able to capture how the anatomical feature variation and the patient inhalation coordination difference can influence the delivered dose in the lungs of the medication.

And then this kind of changes into the results of the medication in the lung and further influence the PBPK simulation results.

So in this case the subject variability and the uncertainty quantification induced by that can be captured all in virtual.

This can provide us a reliable and scalable tool to evaluate how different parameters can influence the plasma concentration of the drugs and how this can further influence the therapeutic effect and adverse risks.

Then, when we talk about AI integration into the critical tools, we always think about the capability of machine learning and deep learning to treat big sets of data.

And this capability can help us to develop fast-running and reliable, reduced-order models, and this kind of models can give us the capability to do faster bioequivalence or comparability evaluation with the capability to do variability studies in a short amount of time.

Those tools are easy to use, and during the inhaler innovation cycle, pharmaceutical companies can generate a lot of insightful data in a short amount of time which can enhance a more efficient communication between FDA and those companies.

Two examples to show the benefits of using CFD as well as AI models.

So this first example is about how we use the CFD-PBPK model to capture the subject-specific variability on the transport deposition and absorption of inhaled medical use cannabis.

So, using three different airway geometries as well as different inhalation profiles from different patients, we were able to capture how those parameters can influence the plasma concentrations of THC in human body.

So those plasma concentration curves give us direct evidence to think about the therapeutic effectiveness of the cannabis as a compound. And also it give us some hints about whether there's adverse risks.

The second example is about how we integrated AI models with CFD simulations to develop this AI-empowered smart inhaler for patient-specific targeted pulmonary drug delivery.

So this kind of smart inhalers are not only collecting patient specific data, but we will use the patient specific data as the input into the AI algorithm to harvest the best position at the mouth to release the medication to achieve the targeted drug delivery to specific lung sites.

This kind of targeted delivery is patient specific and disease specific.

So by achieving this using this new smart inhaler concept, it will definitely enhance the inhalation therapy effectiveness and also at the same time achieve the reduction of side effects.

We are very happy to see that in last two years the priority of research and initiatives released by FDA stress a lot on how to use AI technology. But we still would like to propose a couple of suggestions. The first one is about more special grant opportunities.

We think that the research and development of the AI-empowered smart inhaler technology is important not only for patient data communication, but for the improvement in inhalation therapy effectiveness.

We also think with the new computational techniques and resources, support is needed to develop the international standard for simulation-based testing and evaluation for inhaler innovation.

On the educational and training programs focused on the intersection of CFD, AI and inhaler technology, we would like to see more support so that there will be more resources to help researchers and scientists to build a well-informed workforce which is crucial for sustained innovation and regulation in this field.

Other than that, we think that extending the funding cycles from usually what we see about two years to three to five years is also important. Since the integration of the CFD-PBPK and the reliable AI technology requires sustained research and development beyond typical grant cycles, especially about the preparation of the training and testing data sets.

We hope this presentation brings the awareness of the benefits of CFD-PBPK models, together with AI technologies for accelerating inhaler innovation and improving regulatory science.

Thank you so much again for giving this presentation opportunity.

Moderator: Our next presentation will be delivered by Dr. Maria Malmlof and Dr. Per Gerde, who are directors of projects from Inhalation Sciences.

Maria Malmlof and Per Gerde (Inhalation Sciences): Me and my colleague, Maria Malmlof, would like to propose a study on dissolution and absorption testing of size-fractionated aerosols. This research need is driven by the complex relation between aerosol particle size and lung disposition.

For slowly dissolving substances with fast permeation, a strong relation exists between particle size and lung disposition.

This relation gradually disappears for fast dissolving substances with slow permeation.

Aerosols, these relations are difficult to study, however, because of overlapping kinetics from different aerosol-sized classes.

Separation of such aerosols into narrow disperse size fractions may allow the critical effect of particle size to be better elucidated.

Therefore we see a clear case for the study of dissolution and permeation of fractionated aerosols.

In cascade impactors, high velocity impaction of separated size fractions precludes study of undisturbed kinetics from separated particles.

Aerodynamic separation of aerosol in cyclones, however, into narrow size fractions may allow their release kinetics to be studied following successive re-aerosolization of the different size fractions.

The powder generator of the PreciseInhale system can then be used to re-aerosolize cyclone-separated size fractions.

This is the setup for the size separation of polydisperse aerosols in a three-stage cyclone battery, plus end filter.

The aerosol generator of the PreciseInhale on the left is connected to three cyclones, coupled in series, plus the end filter.

At a flow rate of 25 liters per minute, this gives aerosol cut-off sizes of 5, 2.5 and one micrometers, thus providing four size categories of particles for further study.

This is a tentative scheme for investigating size separated aerosols.

You begin with a polydisperse powder taken through primary aerosolization on the aerosol generator. This gives an aerosol with a wide size distribution.

It is immediately taken through separation in the cyclone battery.

The result is four powder fractions ready for the next step.

After re-aerosolization of each powder fraction, narrow disperse aerosols will be available for further study.

Now, dissolution and permeability experiments can be performed on each of these aerosol fractions.

We propose two suitable systems to evaluate the dissolution and permeability of size separated aerosols.

The first alternative is the Dissolve system, which is an artificial air-blood barrier simulating the dissolution and absorption in the lung of substances primarily on the lipophilic half of the polarity scale.

The second alternative is the isolated, ventilated, and perfused lung of the rat, which, by adding the physiological permeability barriers for hydrophilic substances in the intact lung, effects of membrane and tight junctions can also be studied.

Once you have your experimental results, you would like to advance the kinetic data from the size separated aerosols with a human systemic data set using PBPK models.

One such software package, then, can be used. It's the Mimeticus Preludium from MIS. The Preludium package is already prepared for modeling size separated aerosols.

Experimental data will be then derived from both typical shrinking particle type kinetics as well from atypical dissolution processes of, for example, engineered particles that may rather disintegrate than shrink.

The ultimate goal of the effort is gaining broader understanding of the link between particle size and lung disposition.

Moderator: Our next speaker is Dr. Laleh Golshahi, who is associate professor of Mechanical and Nuclear Engineering from Virginia Commonwealth University.

Laleh Golshahi (Virginia Commonwealth University): Hello! My name is Laleh Golshahi. I'm an associate professor of Mechanical and Pharmaceutical Engineering at VCU. Today we're pleased to discuss enhancing bioequivalence assessment for combination nasal products using anatomically similar nasal models accounting for inter-subject variability.

There is a need for effective testing tools and methods for assessments of regional nasal drug delivery in detail. Methods demonstrating equivalent performance are generally recommended either alone or in combination with other in vitro methods by the USFDA to establish bioequivalence for locally acting nasal suspension drug products with a reference product.

Both the in vitro and in vivo BE studies have limited ability in providing direct measurement of the drug concentration following nasal deposition. Regional nasal deposition in vitro studies offer a new potential way to evaluate performance differences between nasal spray products that may support the BE evaluation of these products across different patient populations.

As listed, there are a number of questions on evaluation of local drug delivery in human subjects. How does inter-subject variability affect the performance? Can we utilize a preclinical product evaluation platform which allows consideration of inter-subject variability while also considering time and cost constraints? If we can have representative nasal anatomies, how could they be used in assessing bioequivalence of nasal products in terms of their drug delivery efficiency to the target regions?

To address these questions, we identified capturing the range of variability in regional drug deposition, following administration of locally acting suspension nasal drug products in adults and children as the primary objective goal. We first identified and processed sinonasal CT scans of 20 adults, 50% female, 50% 50 years old and older within the noted age range to develop 3D models of adult nasal airways that would incorporate a measure of inter-subject variability in testing. A similar approach was taken, and high resolution CT of sinonasal region of 20 healthy pediatric human subjects, 2 to 11 years old, 50% 2 to 6 and 50% developed 3D replicas of nasal airways, and it allows us to capture 40 different nasal geometries for the two age groups.

Anatomically similar nasal models to understand the impact of inter-subject variability on nasal spray performance. Where adults and pediatric subjects are shown. Here two nasal sprays and Flonase Sensimist with different nasal designs, formulation and plume characteristics were used for deposition studies. Similarly, two different products, Nasacort and Flonase were used for deposition studies in pediatric subjects.

Inter-subject variability in nasal drug delivery via nasal sprays is significant. The figure shows drug delivery to the target regions of interest, to the internal nasal valve. The efficiency of delivery to the region of interest, significantly changes from subject to subject, and is also product dependent, as indicated by the given range for the two tested products.

Similarly entering the individual differences in pediatric subjects was found significant, but interestingly delivered to the target region was found more consistent and efficient in children than adults, as indicated by the relatively narrower range of drug delivery efficiency seen in Table one.

Three nasal geometries representing low, mean, and high delivery, were identified for each of the two age groups. The vision is that they can be utilized as evaluation tools prior to individual studies to account for the impact of inter-subject variability in drug delivery, while also considering time and cost constraints.

As seen in the figure, the posterior region of the selected nasal geometries per section into sub-regions to allow assessment of regional drug delivery for a wide range of applications. A spray nasal holder was used for controlled administration. The regional deposition data was used to conduct population bioequivalence (PBE).

The PBE was conducted with the concentration of drug delivery to all nasal regions, following the methods provided in draft guidance on Flonase propionate by FDA. The notice of regulatory constants and BE limits for use. Such assessments early in the development can potentially prevent failure in in vivo studies. However, recommendations on appropriate regulatory constants and BE limits, are warranted.

We utilize the nasal models as tools to address other questions, such as the effect of disease, concentration, or breathing variations. How sensitive is the regional drug delivery to the user-related and administration parameters!

Other remaining considerations are accounting for protective aspects of the nose, such as mucus clearance, and also the increasing interest in intranasal vaccine delivery calls for younger age groups, and also nasal drug platforms for other applications, such as nose to brain would be useful here. I would like to acknowledge everybody contributing to this study, and thank you for your time.

Moderator: Our last, but not least virtual presenter is Dr. Rodrigo Cristofoletti, who's assistant professor from University of Florida.

Rodrigo Cristofoletti (University of Florida): Hello, everyone! I'm very grateful to be given the chance to express my opinion about what research I believe FDA should prioritize to address scientific challenges for generic drug products developing.

We know that co-administration of food with oral drug products can impact drug bioavailability in a formulation-dependent way.

Consequently, FDA recommends that applicants conduct a fed BE study in addition to a fasting BE study, except when the labeling of the reference product states that the product should be taken only on an empty stomach.

So overall, it's necessary to carry out two BE studies under fasting and fed-state conditions.

We do believe that there might be an alternative way based on generating model-integrated evidence for waiving fed BE studies.

This alternative approach is based on integrating in vitro biopharmaceutics data under fasting and fed state conditions, PBPK modeling and virtual clinical trials. In this slide, I'm going to show some results of a preliminary study that was carried out in my group, and it was sponsored by FDA.

Comparing two oral solid dispersions containing itraconazole.

So we have ASD using HPMCAS phthalate, that is, a pH-dependent polymer, and ASD containing HPMCP, that is a pH-independent polymer. So here we are just illustrating the in vitro behavior of both formulations. So they have completely different behaviors in simulated gastric fluid and simulated intestinal fluids.

So first we developed the respective PBPK models under fasting conditions and the models they were able to recapitulate Sporanox and ASD PK under fasting condition, as well as the results of the fasting BE study.

Then this model was applied to anticipate, to recapitulate the food effect on their respective formulations and their respective PBPK models they were able to recapitulate the positive food effect on Sporanox, and they slightly negative food effect on ASD. Now we are working on the manuscript, and we are expecting to have these results published by June.

So the bottom line here for us is that there might be an alternative pathway. This is just one case, and we do believe that more research in oral PBPK modeling is needed to access the generalizability of these findings which may streamline the development of complex oral generic formulations. For example, ASD formulations.

Now, I'd like to switch gears towards lung PBPK modeling.

In lung PBPK modeling, we generally assume the same permeability across bronchial and alveolar epithelium.

However, some recent results that we observed in my group as part of the FDA contract, we observed that the permeability of some drugs across Calu-3 representing bronchial epithelium, and across NCI-H441 representing alveolar epithelium, they do differ. So here in this plot I'm showing the differences between the apparent permeability of budesonide across Calu-3 in green and H441 monolayers. So there is a difference in the permeability. So it violates the general assumption that we are using in lung PBPK models.

Additionally, we also investigated the permeability of the drugs across a 3D organotypic model that was generated with the primary human lung cells. This model is commercialized under the name MucilAir by Epithelix.

So in this model we have different cell lines. It's more like an organotypic model. So we have basal cells, goblet cells secreting mucus, ciliated cells. We do have cilia beating.

And what was very interesting here is that the permeability of budesonide across the MucilAir is much lower than across the Calu-3. So there is really a difference between the permeability in

the 2D and 3D systems. So the bottom line here is that we do believe that more research, assessing segment-dependent absorption across lung epithelium is needed to support the development of lung PBPK models.

Thank you for your attention.

Moderator: So that's the end of our public comment session. I want to thank our public comment speakers for providing valuable inputs to help FDA prioritize the research efforts.

Now we will start our faculty member presentations. Just a reminder to our faculty members, we are currently over time by about 30 minutes, according to our schedule. So you have about maximum 15 minutes to finish your presentation.

Our first speaker is Dr. Liang Zhao. Dr. Zhao is the director of Division of Quantitative Methods and Modeling, Office of Research and Standards, OGD. Dr. Zhao and his team have introduced a broader way of innovative tools in the areas of drug delivery assessment and big data tools, including machine learning to pharmacometrics. With that, Dr. Zhao, the floor is yours.

Liang Zhao (FDA): Yeah, thank you, Lucy, for the introduction. And thank you all. All the public comments are really exciting, and I think we probably this year we received the historical high number of comments, which really reflects the interest and your passion. And although I'm under jet lag from international travel, your ideas really keep me awake. And I really appreciate your input.

So my presentation mainly lets you appreciate in the past how the GDUFA regulatory science program has transformed the regulatory generic drug development and assessment.

And, as Rob mentioned in the past, we have proposed using model-integrated evidence to conduct virtual BE studies, not just to plan a pivotal study, but to serve as pivotal evidence for drug approval.

So the MIE industry meeting pilot was launched in October 1st, 2023. You can also appreciate all the guidelines and research reports at the link shown here.

So this is kind of a brief list of the research priority initiatives for fiscal year 2025. So after this workshop, we are going to have a new list for fiscal year 2024, and you can appreciate that the modeling simulation component MIE component has been integrated in almost every research priority. In the past, we also have two standalone priorities at the end to facilitate the utility of MIE to support demonstration of BE and also expand the use of AI and machine learning tools, as we have heard over many, many public comments on this topic.

In calendar year 2023, the GDUFA regulatory science research program has been impacting both regulatory activities and research activities. In the regulatory activity, you can see, like, we critically contributed to 18 review consults, and I will give you some examples how the research has saved many drugs, otherwise that could be CRLed. We have involved in 43 ANDA meetings and another 6 controlled correspondence, involving modeling simulation, and we have critically contributed to the revision of 9 high-profile BE guidances.

Certainly there are many research activities ongoing both internally and in the form of contracts and grants.

The first example I want to let you appreciate is that the population model-based data imputation have saved the drug. The long-acting injectable medroxyprogesterone acetate injectable suspension.

The problem is that during the pandemic, the PK BE study conducted by the applicant experienced a high volume of missing samples in the mid to late phase in the majority of the subjects that led to the interrupted, truncated AUC profiles.

So with the population PK model, by using the model, we managed to impute the data that have been missing from the curves. And with the imputed data, we calculated and conducted the NCA analysis, and consequently based on the risk assessment using the imputed data, we approved this product.

Certainly this product is supported by the internal research that's been conducted in 2020 titled "Quantitative Clinical Pharmacology Modeling Simulation-Based Support for BE Assessment During the COVID-19 Public Health Emergency." Here also once mentioned that one of the related population PK products, also utilizing AI so conducted by Dr. Bies' lab is where also led to a highly automated tool where you can choose the best population PK model out of one and a half million potential derivatives within several hours.

The second case where the modeling simulation has transformed the regulatory program is that there's a product. We thought the RLD, you know, products being discontinued from the market. In this case there's no generic product with which is bioequivalent to the original RLD. In this case we conducted a comparative in vivo PK study, using a currently available capsule product in the place of the original RLD suspension to establish BE between test and a reference. The model-based scientific bridging allows to identify PK differences between formulations. Therefore the modeling approach is being used to define acceptable BE limit, new BE limit, not necessarily 80 to 125. That taking account of the PK difference between the suspension and a capsule for typical crossover BE study. So this result has been presented by Dr. Calvin Fong in 2020 to ACCP annual meeting. This basically gives us another alternative pathway, when to assess bioequivalence when the RLD product has been discontinued from the market.

The third case goes to the topiramate ER capsule, where there's interesting pattern happened during the alcohol dose dumping study. We found that the test product with it's not you know, failed the dissolution testing when at the present of 20% ethanol, but not at the 5% or 40% of ethanol.

In this case, but the question is, can PBPK model be used to evaluate whether increase the release of the test product at the pH 1.1 with 20% ethanol could significantly impact the systemic exposure compared to the RLD.

The answer is no. So based on the review that derive, you know the review is based on the PK PBPK modeling. To wrap the data, we concluded that there's no significant safety concern arising from the ADS study with higher release from the test product. A sad finding from this practice is that we identify the bibasic dissolution profile can mimic the drug release in different GI segments of the stomach, and therefore is more is about predictive dissolution compared to the dissolution at the pH 1.1 alone.

So these products certainly kind of we heavily influenced by the ongoing research from a doctor at the Northwestern University.

So another product that PBPK modeling simulation has saved it from CRL is the mesalamine delayed release tablet. It's indicated for the mildly to moderately active ulcerative colitis.

The problem with this product is that the dissolution conversion failed at a pH 6.8 and a 6.9 buffer in. But at the pH dissolution profile have passed, or at other pH levels. In this case, can we use PBPK model to evaluate the risk about inequivalence for the test product at the site of action with the colon with the failing dissolution comparison at the two pH levels.

So we developed the PBPK model and evaluated with applicants' supplied data under the colon mark was predicted to be similar between RLD and a test product.

So the impact of the model is that, the PBPK model predictions, in combination with other scientific review evidence supported the approval of this generic, this test, this generic application.

This is also benefited from the ongoing two ongoing PBPK projects for the yeah locally acting products. Certainly, we thought, that's kind of a knowledge accumulation and exchange. It won't happen this quickly.

Not only the modeling have saved many products from a being CRLed, it can heavily influenced the PSG revision. So the first one another example is the diclofenac gel.

So the value creation is that the modeling simulation supported the revision of the PSG, option one, which now does not include IVPT BE or an in vivo PK BE study. So this is a kind of a very high cost of saving for future applicant.

These practice with the party to buy 5 grants on the 5 grants, either ongoing or happening in the past.

Another we have been seeing CFD modeling on a PBPK modelings here. I want to show that a CFD and a PBPK modeling have really been implemented and consolidated in the PSG guidance language.

So with the CFD PBPK modeling already with our internal effort, the direct research have the support, the first ever inclusion of a mechanistic modeling language in a PSG for an orally inhaled drug product that is intended to facilitate the use modeling to determine the relevant BE limit, or recommended in virtual and in vivo studies.

By following the detailed guidance of doing. you have the and PBPK modeling.

We have encountered many interesting questions is going to be one of the making very high impact in the future, especially in this challenging, orally inhaled drug, but we couldn't assessment area.

So this improvement was supported by by 8 external grants and contracts, as well as internal research.

The external contract was mainly on model credibility, statistical method for comparison over the result. Original lung geometry, subdivision.

So in the rest of the panel discussion, we want to seek your comments on the following issues.

We want to see your potential further thoughts on facilitating the utility of MIE to support demonstration of a BE.

For example, BE space for individual evaluations. What could it be the new type of a design for oral quality and long-acting injectables best practices for virtual BE studies, how to validate the BE the how to validate the BE the modeling of practice for regulatory use.

Barriers can also increase natural mitigation strategies, assessment of a complex activity ingredient, as Rob mentioned in the morning. That will be audio nucleotide and a peptide.

We are also expecting your comment. We also welcome your comment in in terms of enhancing efficiency of BE approaches for complex routes of delivery.

Enhancing the efficiency of the equivalence approaches for complex drug device combinations, for example, more efficient human factors analysis.

How come your further common ability to BE studies for oral under non oral products, for example, bio waivers, always hosted with many, many high fraction of generic applications.

At the last and a one further one. Your further comment on AI or machine learning tools for generic drug development. Here, I want to mention. Also, if you have a thought on in silico immunogenicity prediction, I think that's another catchy topic which are kind of a left out from this this presentation with that. Want to pass the podium to the next presenter. Thank you.

Moderator: Thank you, Dr. Liang, for the presentation, so we can move to our next speaker, Dr. William Dr. Ganley. He's going to talk about PBPK modeling for locally acting, sorry for integration of simulation in vitro and the clinical methods support complex drug product development.

Dr. Ganley is a physical chemist with a PhD from University of Bristol in UK. He started his career as a postdoc in pharmaceutical surface science lab at University of Bath, UK. He's focused mainly on advancing physical characterization and simulation techniques for dry powder inhaler formulations, aiming to better understand the connection between physical attributes and delivery to the patients.

William Ganley (University of Bristol): Okay, great thanks very much. Thank you for the introduction and thanks a lot for the opportunity to stand up here today and talk to you to you all about some of the ideas that I've got for advancing research in in generic drug product development. So my presentation is going to be focused on the integration of simulations and in silico tools with in vitro and clinical studies.

And I think the key message that I'd like to get across is that I and I think this has become clear as of as we've listened to a lot of the presentations and ideas and some of the research projects we've heard about today is there's a great deal of the basic research. And I mean the kind of fundamental tech techniques and technologies and best practices. For in silico methods, have already been established.

So what I want to kind of make a call for is an increase in the number of collaborative and crosscutting research projects which bring together some of the advanced in vitro techniques

and clinical methodologies within silico techniques that we've been developing as well, that produce even more benefit. And I think this will allows to yeah, to get the most value from these techniques that we've been developing.

So in terms of what in silico techniques can be used for, they generally fall into 2 buckets. And so these are our development tools development tools which allow us to develop genetic drug products with the right, the right product, profiles and the kinds of things that we can we talk about. Here are things like formulation, safe spaces, where we can use modeling and simulation to kind of back out a an in vitro or performance product profile that we can use as a target to kind of de-risk.

The clinical performance of the product. And then also there is sensitivity analysis. And this is where we can see which of those levers in product development we can pull to really move the clinical profile around and make sure that we're focusing our attention on the most important factors.

Then on the other side of that, we have regulatory tools. So this is tools that can be used to to support regulatory decision making and make that final assessment of bioequivalence under the way of evidence approach, and the kinds of things that we can do here are use of virtual clinical studies. This is where we would develop a cohort of virtual patients, either as digital twins or as or as generated patients.

and there we can run tens, hundreds, or even thousands of repeats of a clinical study, and understand the variability and the probability of success.
And these can be used to support bioequivalent determinations on their own, or be used to derisk or reduce the burden of a clinical study and a bioequivalence assessment.

The other thing that we can consider is in vitro and viva correlations. This is related to something that Gunther was talking about not so long ago, where we can use modeling and simulation to come up with more than simple linear regression in terms of in vitro and bioequivalence correlations and really pull out those important drug product performance attributes that allow us to understand the clinical performance, and these may be it may be possible to do these in the absence of modeling and simulation, or it may be that modeling and simulation forms a key part of making these assessments.

and we've seen quite a lot of success. As I said in the opening of my presentation, in the use of modeling and simulation to kind of augment in vitro and clinical studies. Now I show some examples here. Many of these have come out of GDUFA funded research. The 1st on the left hand side is a study that was done at Princeton University on understanding the aerosolization properties of dry powder inhalers. So these are incredibly complex and chaotic systems with lots of particle interaction dynamics that are very difficult to understand. And we've for years have been measuring the performance properties of these things, but not necessarily understanding how they how they come about so using modeling and simulation to really understand those aerosolization dynamics right in that dry powder inhaler device. And then using this to understand what happens when we go to measure these in in vitro has really assisted our understanding of how these, how these inhaler devices work and can add a lot of context and a lot of confidence to the in vitro data that we put in generic drug submissions.

Of course. We can also apply these things to more biological systems. So there's been some quite a lot of work done to come up with in silico representations of cell epithelia. So we've heard in quite a few of the public comments in this session that, particularly for inhaled products,

the permeability through the epithelium is quite difficult to understand, and that there's not always great correlation between immortalized cell lines and what happens in in vivo so using modeling and simulation to kind of come up with a representation of this and then up validating it against clinical data or in vitro data is something that's proving quite. quite promising

and then getting even closer to clinics. There's been a fair amount of work in clinical imaging studies. So this is where we can use computational fluid dynamics to predict the deposition of an aerosol in the lung, and this can be validated against one type of product and then extrapolated to another. So the particular study that I'm citing here. Verified the deposition. Predictions for one suspension metered dose inhaler and then extrapolated that to a different metered dose inhaler with an addition, an additional API, to demonstrate that there was no difference to the regional exposure of that product. When the when the additional API was added.

and then in terms of pharmacokinetic studies. So there's some scenarios, particularly from ophthalmics, where the data that you get from the pharmacokinetic studies is by its very nature quite sparse.

And population PK. Simulations have been used to run model-informed bootstrapping exercises here to squeeze kind of more insight or more value from these sparse data sets and allow bioequivalence determinations to be to be done even with the absence of quite a lot. The data and Liang mentioned a kind of similar example with the Covid issue in this previous talk. And I think there's a lot more scope to use these kinds of data analysis techniques to reduce the burden or reduce requirements for clinical studies using mechanistic modeling and simulation in the future. So this is kind of an area that I think is worth pursuing.

So the what I will really want us to do, and what I think the focus of some future research in this area should be, is coming up with frameworks to bring this all together, and essentially going through and filling some of the gaps that we have in the diff for the different dosage forms in the different areas to allow this to happen. And I I think this could happen in in 4 key ways. So the 1st is continuing to develop advanced in vitro tools. We've heard a lot about these today.

But what's really important is these in vitro tools must have the ability to extrapolate to local exposure at the site of action for complex, generic, complex generic products.

And one key way that this could be done is by building in silicon models alongside these that can be used to do that extrapolation into a full physiological model. So you might end up with a situation where you can measure something in vitro and then use a modeling and simulation approach to extrapolate this up into a whole body, fully physiological, physiologically based pharmacokinetic model, and then use that to run some virtual BE studies.

Tying this all together, of course, is credibility. So we've we heard from the model master file meeting at the CRCG earlier this month that the regulatory thinking in terms of validation of models is moving quite quickly. Which is a great thing.

But one thing that we've got to bear in mind is that there are lots of different uses of modeling in generic drug product submissions. And there's a sliding scale of required credibility. So we need to understand better what level of verification and validation is required for all of these different types, of all of these different utilities of the models.

And then I've already spoken to the clinical studies a little bit where we can use modeling and simulation to either reduce requirements or improve our statistical analysis of these data.

So the last few slides, I'll go through some specific examples of research areas that I think could fill some of these gaps that I'm talking about. So here in terms of the in vitro tools, quite a lot of interest in flow, particularly for areas like ophthalmics and orally inhaled and nasal, where you have a mucus layer or some kind of liquid barrier. One key interest of mine personally, is in mucociliary clearance assays. I think I've yet to see a convincing one that's allowed me to input some data from it into a PBPK model, for example. So more area, more research into how these in vitro and in silica techniques come together would be useful. And then another important factor, I think, is in model structuring. So we've seen some incredibly detailed models with lots of differential equations on slides and things today. And I think one question that I like to think about when I'm doing some model building is, how detailed do we need to be? I think we need to be as detailed as is necessary to solve the problem that we're asking, but probably no more. And I, I think that's something that as modelers quite often, we just build the most complex model we can and if it solves the problem great, but sometimes there's a lot of wasted resource in terms of making something that's a little bit over complicated. So I think there's some thinking that we can. We can put in there

in terms of simulation of local sites or disease states. I think there's some work that modeling can do to help us here. Particularly in the bridging between simulate sorry clinical studies in healthies to disease patients.

So if there's a way to select particular disease, state characteristics and then simulate those we could potentially bridge or extrapolate some of our clinical studies in health healthy volunteers to disease patients to reduce the burden or the requirement of clinical studies in in patients. When we're looking for generic drug product submissions. And an example of that might be an assistive fibrosis patient where we have a good amount of knowledge of how the mucous layer differs in in those patients compared to healthy volunteers, and can use that in our mechanistic modeling.

model risk is another important factor. And I think one of the important one of the most important things here is the availability of data for validation of models. We've heard a lot about artificial intelligence today. And there's a lot of data that's required to build those. But we also require data to build our mechanistic models. I think in one of our preparation sessions for this Liang made an interesting point. The modelers are typically quite passive.

We wait for the data to come to us and then use it in our models. And I think we have an opportunity now that information and data has become more part of the conversation to actually take control of this and do some more work in terms of the governance of this data so that it's more accessible for people to use to build models to solve problems.

And the last part that, I wanna just touch on is in silico clinical trials. So we speak a lot about virtual BE. But I think there's more work we can do in terms of patient selection in terms of how we generate our cohorts. The use of digital human digital twins as well as synthetically generated patients, and how that might be done.

And then, of course, for statistics. So it's been great to see the revised product, specific guidances inhaled that have come out this year, which has suggested that we can use modeling and simulation to define the limits, or better inform the limits, for bioequivalent studies. And I

think there's a definitely, more definitely, a possibility that could be used more widely across lots and lots of different bioequivalent studies that are done both in vitro and in vivo

so just to wrap up I'll show kind of my 4 step program or the 4 key attributes that I think we should. We should consider in to bring the in silico in vitro and clinical studies together to improve drug generic drug product development. And I look forward to the panel discussion later. Thank you very much.

Moderator: Thank you, Dr. Ganley. Our next speaker is Dr. Jessica Spires. Dr. Spires is a principal scientist at Simulation Plus. She is focused on physiologically based pharmacokinetic modeling of non-oral routes of administration, including dermal, ocular, and pulmonary administration.

Jessica Spires (Simulation Plus): Thank you so much. I'm very happy to be here.

I'd like to start off my presentation by giving some praise to FDA. You all have really done a lot of investment into looking at the modeling and the simulation. These are just giving some examples, just purely looking at the collaborations that we that we have that are currently active with Simulation Plus you can see here, we've got, I think, 5 different separate grants looking at different locally acting areas so ocular oral cavity, pulmonary, dermal model, as well as the locally acting drugs in the GI.

We also have the grant looking at the long acting injectables. There's a lot of overlap there with the locally acting products. Looking at the modified release as well, looking at some of the complex formulations, and of course pulling all of this together is improving our virtual bioequivalent trial workflows. So that's something that we've been really happy with.

But there are always some gaps, and there are always some places where we see things where we'd like to see some increased investment from the FDA. I'll be talking about 2 major areas in this case. 1st one is looking at like the best ways to extrapolate from the measurements and in vitro data to generate the reliable in vivo predictions in particular. Looking at this in the context of the non oral routes of administration.

and, generally speaking, we're not as advanced in these areas as we are with the oral route. So sometimes we still have these questions. You know what are the best in vitro assays to perform. You know there are different types of measurements that we can do what are the most important ones to take. This can be different, according to your API, according to your formulation, according to your route of administration.

How do the parameters need to be adjusted when used in vivo in vivo? A lot of times we can't just take the number and just swap it in. You know, we have to make some adjustment depending on whether we're modeling the in vitro case or the in vivo case.

And of course, we also have the question, are there new in vitro assays or measurements that will be more useful? Okay, another issue where we start to see some issues in some cases is extrapolating between different species and most of the time we're going for the preclinical species to human. In some cases we have the multiple preclinical species. So even if we have a good understanding of what's happening in the human case, our understanding in the preclinical species may not be as advanced.

So how well do we understand differences between absorption, distribution, and clearance at the local sites of application? As well as kind of maybe moving beyond the pharmacokinetics, and also looking at things like the pharmacodynamics, and how those might be different between the species. Again, looking at these local sites of application. Okay?

And really kind of the common factor between both of these is, of course, the question that we always have the whole reason why we do modeling. In the 1st place, how do we know when the models that we've developed can be extended to new scenarios? We're moving between species. We're moving between different types of experiments.

And do we know what adjustments to make?

So I'll be talking about this through lens of 2 different case studies. I'll start off looking at an ocular case. In particular. For those of you who are familiar. Glaucoma is a disorder that's going to be elevating the intraocular pressure in the eye long term that leads to vision loss.

But we can treat this by using compounds like latanoprost to modify the aqueous humor dynamic. So we want to use this to decrease the intraocular pressure to slow or prevent the vision loss from glaucoma. Okay?

Typically when we're looking at the topically applied ocular compounds, rabbits are usually the animal model that's used. That they have a very good comparison of the PK between the rabbits and the human. But for the PD effects they may not be as sensitive to a drugs effect. Okay, so we're thinking about scaling of PK and PD, it may require multiple species for these types of drug products. And no surprise with latanoprost is one of these products where we see this issue. Okay?

So I'll mention as well. I'll have 2 slides of citations at the end, because it got a little unreasonable. Okay? So if you look at the plot in here, you'll see highlighted here. This is looking at the effect of the intraocular of latanoprost on the intraocular pressure in the rabbit. And we see essentially no difference in this case. Okay, and if you look into the literature, you'll see that this effect of latanoprost to lower the intraocular pressure is something that we primarily see in the primates.

So for this reason the monkey is clearly the species of choice to investigate latanoprost mediated IOP reduction.

So we started off, using the rabbit model to build our PK, we had, I think, 5 different studies in this case. And you can see the set of graphs up here. We were able to get to build a model using GastroPlus ocular model. We were able to build a good model that represented the PK for all 5 of these studies. Pretty well. Okay.

we're also able to apply this model to the monkey, and you can see here over 3 different studies, and we had a good match to the monkey PK as well, okay. And then, finally, we were able to apply this to 3 different studies, looking at the aqueous humor in the humans, and you can see that the model that we built worked very well across all 3 of these species.

So next, we use this now that we have our monkey PK model and our human PK model. We want to use this to investigate the PD model of latanoprost.

So I won't get too far into the details here. The PD model in this case is a little bit complex. The reason for that is because the IOP often has a circadian rhythm sort of to have that, baseline. The model has to be a little more complex.

and you can see that in this case we're able to fit the 2 key. Sorry the 2 key parameters, Emax and EC50. Okay. And we are able to get a very nice match of the experimental data with these fitted parameters.

So the final step, of course, is to apply this to the to the human case. Okay? And in this case we were able to get a match. We were not able to get a match, using the same parameters that we use for the PD. Model in the monkey, we were able to use the same EC50. But we had to adjust our Emax value. Okay? And we saw a difference there. Some of y'all may have noticed the foreshadowing in the previous slide that you see some large species differences in the response for this compound.

Now, this is a very specific example, of course, but a lot of the concerns that it raises are concerns that we generally see with modeling of the locally acting drug products and the non oral routes of administration. Okay.

1st question, what's the best preclinical species for modeling the PK for my compound at my site of action.

you know, in some cases, you know, if I'm doing a topical ocular formulation. I'm probably gonna look at the rabbit first. But for a lot of the other routes of administration this choice may not be as straightforward. And of course, even when you're looking at the ocular route, there may be cases where you want to use a different species than the rabbit. Okay, next question might be, what's the best preclinical species for modeling? PD. For my compound at my site of action? This might have a different answer than the best species to model my PK.

and then, of course, the 3rd question is, is there any further adjustment in the PK or PD that's needed when moving for the preclinical species to the human. Okay, in this case our PK worked very well across multiple species. But for our PD, we needed some adjustment. Okay? And how would how can we know whether this is needed ahead of time?

The second case that I'll talk about will be looking at a modeling of the topical drug products. Permeation through the skin is going to be affected by a lot of different factors. I could probably spend a whole day just talking about different things that happen here, whether it's under the in vitro conditions, where you have the in vitro skin samples, what's the source of the skin. Was it ever frozen? How was it prepared? What were the laboratory conditions?

And even in the in vivo case, as well? You know what part of the body is it being applied to? What are the conditions that's being applied under? You know, just a lot of different things can be affecting this.

Okay, in addition to this, the topically applied drug products are often very complex and may not be as well characterized as we might hope. The solubility of the API and the particle is going to be important. Viscosity, the volatility, the excipient effects, you know. Of course, you're actually manufacturing this, you know, it has to smell nice. It has to have good material properties, you know. You might have an adhesive, so it has to physically stick to the skin. There's a lot of different things that are going on.

So in this case I'll be talking in particular about acyclovir. This is an antiviral drug. When it's used topically, it's usually treating the symptoms of herpes and things like that.

In this case we had some in vitro penetration data to characterize the permeation from Zovirax cream in vitro. And then we also had some in vivo tape stripping data where you're actually able to look at the amounts are in the stratum corneum in order to characterize the in vivo absorption. Okay? So I'll be talking about this case.

So to start off here. Of course we knew we knew some things about the characteristics of our compound. We also were very fortunate in this case that we had a full characterization of the Zovirax cream that's been published. That was really great to have. Okay. So we're able to put all this together to generate a set of a set of values for the acyclovir, describing the character, its characteristics in the formulation as well as its characteristics in the skin that we are able to use with our dermal model.

Most of the time. In this case this would be the point where I go into a whole lot of detail about how do we generate the properties, the different product, the different properties of the API within the formulation? What if the parameters are different than we think that they are looking at the sensitivity and different things like that? We're a little bit fortunate in this case. If you have any familiar with Zovirax cream, 95% of the acyclovir in this cream is undissolved. Okay? So

so basically, there's no sensitivity to any formulation parameter, no matter, unless you reduce the dose by like 95% or more. You're always at the maximum thermodynamic activity. So that makes us a nice example for this case, because we can really just have kind of a basic baseline set of formulation parameters and really focus on our modeling of the permeability once it actually gets into this.

So the 1st thing that we did in this case was to use this IVPT data as you can see here, this is going to be the points here. This was 2 experiments from the same study. And this is looking at the this particular is looking at the flux. Okay? And what we did here was we use this to adjust the stratum corneum permeability.

So a few notes here, stratum corneum, is the major barrier for the skin. So most of the time when you're having some issues characterizing the permeability, you're going to look at the stratum corneum first.

Another aspect. Unfortunately, we have to get a little bit into the weeds here to explain what's going on. In this case we use the Potts and Guy model as our baseline model to predict the permeability through the stratum corneum. And this is a PBPK internal model that's been published. Okay? But really this permeability, you can divide into 2 parts a diffusivity and a partition coefficient. So if you multiply these and divide them by the thickness you get the permeability.

So what this means is that different combinations of diffusivity and partition coefficient can lead to the same permeability. And what you'll see if you go into the modeling is that this can have very different impacts on the disposition in the skin while having maintaining the same overall permeability. That's the reason why we separate them in the model.

So we did in this case was we had a baseline value where we have this predicted permeability. We make some assumption for partition coefficient, you know, and then, of course, the remainder is going to be diffusivity.

And so that's what the blue line was here. Okay? And you can see that in this case, after about 24 h, it looks okay, you know. But for that 1st 24 h period, and particularly looking at this peak here, we really weren't capturing it at all. We were really underestimating here. Okay.

So the second thing that we said was, okay, you know, keeping this predicted permeability the same. Let's look at different combinations of the diffusivity and partition coefficient to see how close we can get while maintaining that same overall permeability. Okay?

And the red line here was basically kind of the best case that we could get with that same permeability. We increased the diffusivity, decreased the partition coefficient, same permeability, and you can see there's a little bit of improvement here. But overall, we still weren't getting close to what we expect to be seeing for those 1st 12 or 18 h.

The final step here is, we said. You know, we actually don't expect the skin permeability to be the same for the in vitro and the in vivo conditions. You know, we have this Potts and Guy model. It's hopefully predicting the in vivo skin. So for the in vitro skin, the permeability may be higher. That's very common. Okay?

So what we did in this case, we said, Okay, let's let the permeability be, whatever it is. In this case we let the diffusivity stay the same, and then we started reducing the partition coefficient, and we till we got kind of the best model that we could, and that was the green line. In this case you can see, this was going to be a much closer match to the experimental data.

So okay, we've got our best in vitro model. Okay.

second step is to build our in vivo model. Okay? And then we can look at these 2 models and compare them and see if we can start to both, draw some conclusions, built some correlations.

So in the case of the in vivo model, we had some tape stripping data. So this was the actual amounts that were in the stratum corneum. The points here are going to be the different subjects

and the black lines that you see here with the geometric mean of the experimental data. So that's what we were kind of trying to get close to

again. We started with that baseline Potts and Guy model, making some assumptions about the initial values here, and that that what we got there was the blue line in these cases. Okay, so you know, we're in the right ballpark. It's not completely off. But for all of these we were underestimating. We were really at the lower end of the range that we saw with the experimental data.

Second step, the same thing that we did for the in vitro data. We kept that same predicted permeability, and we started making adjustments. And the improved model that you'll see, here was with the red line here. So we're able to get a lot closer to the geometric mean that was great.

The part that's a bit confusing in this case was that we actually had to make the opposite changes to the diffusivity and partition coefficient as we did for the in vitro case. So we actually had to reduce the diffusivity and increase the partition coefficient in order to match the in vivo case.

So now we're just kind of so we have a manuscript about this that will hopefully be published soon. We go into some more detail.

but you can see how we have a lot of questions here about how we should move forward and how we can understand the relationship between the in vitro penetration testing and the in V, what's happening in vivo.

So again, zooming out a little bit. You know, this is a very specific case. But again, we have some general concerns that we can look at here.

How well do I understand my formulation, you know. Do I know what its critical attributes are? Or in this case, that there were no critical attributes. How do I measure or calculate these?

What can my in vitro data tell me about my local PK at my site of action. And 3, rd what adjustments do I need to make when moving to models of in vivo PK at my site of action? These are all questions that are very common again for these locally acting drug products. Where we would really appreciate some more investment from the FDA to start to get some answers.

okay, so I'm a little bit over time, I know. So this is just a general summary. 2 aspects that I spoke about. I also have a 3rd example here. Didn't have enough time to talk about it. But a better understanding of the complex dosage forms would be very useful. I would say. In this case FDA is investing a lot. So I didn't need to use a whole full case study for it. But that's also something that's on our radar where we could still use even more investment looking at the complex dosage forms for these products.

So I think that's it for me. Thank you very much. Folks at the simulations plus working on these projects. Folks working at with us at the FDA. Really helpful.

Moderator: So we have one more talk, and then we can open the discussion.

So let us welcome Dr. Jan de Backer and for his presentation about the digital twins and in silico trials to support the approval process of complex generics.

Dr. de Backer graduated from Delft University of Technology in Netherlands as Aerospace engineer, and then he attained his Master's degree in aerodynamics, and specialized in applied biomedical, computational fluid dynamics leading to his Ph. D. From the University of Antwerp in Belgium.

Dr. de Backer has received several awards for his innovative research in the field of airway, modeling in respiratory and sleep medicine.

Jan de Backer (Fluidda): Thank you so much. Last talk before the panel. So hopefully, you're still there, and thanks so much for sticking around.

It's really my pleasure to talk to you about. Digital twins. And then how we can use in silico trials to support the approval process of complex generics.

Specifically, what I think is a very interesting evolution towards quantitative medicine.

Before we go into that, I wanted to take a step back and see where we come from

so approximately before 2016. Roughly, if you would talk about modeling and simulation healthcare, it's pretty much what this image represents. So you do have a model in a simulation tool that represents some features of a human, but it's definitely not perfect. And if you talk to healthcare professionals about it, you get things like patients aren't robots. Your models are nice, but it's not reality.

impressive technology, but it misses. And then you usually get a whole list of things that's not included in the modeling in the simulation.

but fast forward to today, and especially then they really zone out. If you talk about modeling and simulation back, then. But if you fast forward to. Today.

we have very different technologies. The technologies have advanced quite substantially. These are not your grandma's models anymore. These are really high performance algorithms that when applied correctly. They do represent accurately human health, and it's likely we'll see human disease as well.

And very recently we heard about it this morning the FDA started the center of excellence for quantitative medicine.

where they focus also on drug development, regulatory decision making and even patient care. And if you say that the FDA is involved, and also the healthcare professionals tend to re-engage, which I think is very important.

So for today's talk, we'll be looking at how to using silicon models in combination within vitro and PK. Studies to obtain a bio waiver for the clinical endpoint study. So as we heard before this morning from Dr. Lionberger, or a very important topic where we think we can make great advances to get these drugs easier on the market and closer to the patients.

So the 3 pillars for bioequivalent studies, as we know. 1st of all, we have a device and formulation where we use the in vitro tests to show that the tests and the reference are similar

systemic exposure. Typically, we use the clinical pharmacokinetic studies to compare the 2,

then, for the local exposure. It's often the clinical endpoint study that's still indicated. But as we heard before, it's a very expensive way of looking at local exposure, and it takes a long time, and the FEV1 is also a very flawed endpoint that doesn't necessarily reflect a lot of the local exposure.

So we want to see if we can move towards, let's say, a more modern approach where we use in silico deposition studies to understand whether test and reference formulations have similar local exposures.

and, as we've heard before, I think the generation of visionary leaders now at the FDA is increasingly including the language, for in silico studies into the product, specific guidances with this one for formoterol and glycopyrrolate.

where the models can be used for virtual bio-equivalent simulations. And we'll show you some examples of how we interpret that

established by relevant, relevant limits. For bioequivalence very important, because often, as you probably know, it's not that easy to fall between those limits. So if you can, using silicon to support the argument there, I think it will facilitate some of these approvals. And then, obviously, the CFD to look at central and peripheral deposition.

So the virtual bioequivalent studies using these digital twins, how can we get to that point where we really have what we have is the digital equivalent of the clinical study.

How to do that is to make sure we have the digital equivalent of the key parameters that drive the deposition for inhaled drugs.

In this case the large groups are the device, the drug formulation, ventilation, profiling, and very importantly, the lung structure and the function.

So for the device, we can use the computer aided geometries, or we can reverse engineer the device to get the computer a version of it. The digital version

for the drug formulation we have the in vitro characterization

inhalation profiling. We typically use an in vivo study where we see how the patient inhales through the device under investigation, and we obviously record it in a digital way. So we digitize the inhalation profile

and for the lung structure, the lung function. We use what we call functional respiratory imaging.

So functional respiratory imaging starts from the high resolution. CT, scans, and over the last 20 years or so we collected, I think, near 20,000 of the scans across several lung diseases.

and so we go way beyond the visual interpretation by radiologists. So what we do is we convert these 2D CT slices into 3D. Reconstructions of anatomical structures.

So you can see obviously more. But you can quantify it so you can use the numbers to assess the regional expression of the disease

by taking A CT scans at inspiration and expiration. We can add functionality to these images, so we can look at regional ventilation, which is obviously important when we try to understand the path of inhaled particles and the deposition of inhaled particles. We can also look at airway resistance.

and by combining it all we look at the deposition of these inhaled particles

as we heard before. Validation is a very important element to it. So there is quite a large body of evidence showing that if we look at total lung dose, the CFD-based deposition. Using these patient-specific geometries provides quite accurate results.

There's also an increasing body of evidence showing that on a lobar level there is a good agreement with what you would get from the CFD. Of deposition compared to what you would have from the SPECT. CT data

quite grateful for the FDA to be working together under this grant where we go even one step further, where we like to see validation on an airway branching level. That's a that's a grant that started last year. We're making good progress with that.

So with this approach, you do have a lot of insights into the different aspects of the disease of the deposition, the inhalation, profile, etc. So you have a lot of variables.

Then one of the obvious questions is, are all these variables equally important, or some more important than others.

especially if we try to compare 2 products. That's the reference. We know they're not the same.

even though that if you compare the reference with the reference. Often it's not the same. So we have to understand if the differences that we observe are they potentially, clinically relevant.

And in order to get a little feel for that. So what we did is we over the last years we've done thousands and thousands of CFD simulations.

So we looked at a Monte Carlo simulation to see what are the key drivers for deposition.

So, for instance, for dry powder inhalers, we have a list of the input parameters from the fine particle fraction to the patient. Specific parameters like airway volumes, airway areas, etc. So we can see what is quite influential, and which are the parameters that might not matter so much when it comes to either assessing intrathoracic deposition or peripheral deposition, because, remember, the guidance is now ask us to understand, okay, what is central versus peripheral deposition? So what is the regional exposure to the drug?

And we see, for instance, for dry powder inhalers that obviously fine particle fraction is important, but also airway volumes and airway areas.

If you look at some of these reconstructions, it's quite clear that airways from COPD. Patients and asthmatic patients are very different from healthy volunteers.

If we look at cystic fibrosis or idiopathic pulmonary fibrosis, it's even more pronounced.

So it's important that if we want to go towards the digital equivalent of a clinical trial, we include these aspects in the quantitative medicine approach

we look at metered dose inhalers. You see, for instance, the peak flow not surprisingly. It's quite influential to assess intrathoracic deposition and peripheral deposition. You see that here, if you look at the flow patterns that are generated by MDIs and DPIs in the upper airway in the mouth region, you see that the turbulence induced by these different devices is quite different. Also, as a function of the peak inhalation flow rate.

So the deposition in the upper airways quite influential, obviously, for what ends up in the lungs in the lower airways, and you also see that the narrowness of the upper airway is quite important to understand the regional exposure to the drug

for nebulizers. Not surprisingly, things like the FRC. Lobe volume, which is a measure for air trapping, a dynamic hyperinflation and ventilation mean flow they're very important parameters. And this is what you see here. This, this is an IPF patient, where you can clearly see that the upper lobes

are more ventilated in the lower lobes. That's because the IPF disease typically starts in the lower lobe. So these lower lobes are more affected. The upper lobes tend to take over in terms of regional ventilation, but also affects, of course, where the particles end up. If you would make an inhaled formulation for IPF

for validation. I think there is already a good level of evidence for total lung dose and lobar dose, but we would like to take it one step further. So we are currently engaging in performing a prospective validation study. Where we look at 2 formulations that are substantially different. So large particles

versus small particles, we are enrolling in the gamma scintigraphy, study healthy volunteers as well as diseased patients. And in the same cohort we're doing the CT scans the FRI deposition. So the CFD based deposition and the gamma scintigraphy, and we're bringing it all together under the SMARTTRACK umbrella in collaboration with Nanopharm, so that we can have an end to end. Validation of this in silico approach to further support the use of it in these regulatory files.

So what are some of the future directions that we feel are important to consider. And I think this is true, for the broader AI/ML field is that we have to avoid biases in the training sets.

We have to ensure diversity in things like the HRCT. Scans, inhalation, profiling, and so on, so that we don't all end up with all white males in our training sets, but it's really a proper diversity inclusion criteria that we can have there

during the model master file workshop. We had some discussions on eventually seeing if we can even replace the in vivo PK studies with some of these in silico methods. If you think about it, even things like the HRCT. Scan, where we all think it's a measurement. We think it's a measurement of what happens in the lungs. It's actually a model. You have detectors, you have radiation. And you have a computer computed tomography that creates a model that we think is a representation of the lungs.

But the difference between a model and a measurement, in my opinion, is the level to which we believe that the technology provides accurate solutions. So if we can build on the credibility of these models, then I think we can increase the application, including potentially replacing some of these in vivo PK studies. If the evidence would support it. I think further discussions around the creation of the model master file to streamline the approval process is quite important, because I do think that will bring more credibility, more validation, and I think a good basis for further discussion to see how we can further start using these models going forward in summary. I think we're at the dawn of a very exciting period, where I think we'll see a lot of innovation. I think a lot of improvement in the drug development. I think starting the center for quantitative medicine is a very powerful signal towards the industry. So I think it's really the right

direction, and I'm looking forward to working with all of you to make sure we can get better drugs to the patients that deserve them. Thank you so much.

Panel Discussion

Moderator: Thank you, Dr. de Backer. I think I really need to stretch.

So let's give a big round of applause for all our faculty members as well as our public comment speakers for their very insightful presentation.

and also thank you all for still staying with us. It's we apologize for running late for this session.

Okay, let's quickly jump into our panel session.

I will start with from the with the 1st question. So Dr. Zhao delivered a very convincing message that quantitative modeling and the modeling plays a role from early to late stages of the life cycle of generic products.

FDA strives to provide practical product, specific guidance to really get the industry in product development in the case of complex generics, without the guidance either due to a knowledge gap or the applicant wants to pursue an alternative BE approach. The use of quantitative methods. Modeling is becoming a more common and important element in justifying those alternative approaches. So the question to the panel members is in terms of the modeling simulation tools. What additional research do you believe would have the most significant impact to advance the development and enhance the application of tools to modernize generic drug development and bioequivalence assessment. So today, we heard a lot, we heard the best practice and model validation and sharing for the assessment. We heard PBPK model extrapolation from individual to individual as well as across different species. We heard the request to collect additional in vitro data for building PBPK models. We heard some novel designs of course, associated with statistical approaches. We also heard some talk on the BE space for individual characteristics. So I mean, this is just something I took as my personal note. So I really want to hear from our panel members. And what research do you believe has the most significant impact?

I'm going to start from our external experts first.

So, Ping, can we start from you? I know, like Bill and Melinda Gates Foundation, heavily involved in supporting the underserved area and the communities, probably mostly in the new drug development. But you have a lot of open dialogue with a lot of different stakeholders. So want to hear some thoughts from you.

Ping Zhao (Bill and Melinda Gates Foundation): Thank you, Lucy. Really a great pleasure to be here. Even though our organization mainly deals with the development of new drugs, new molecules, new vaccines in in terms of the application of quantitative methods in generic product development, sponsored by or supported by the Gates foundation. This is very new. So actually, one thing I would like to sort of to see, for the, for the upcoming years would be the expansion of the program, so that you can increase the awareness. I know that OGD. Has done a tremendous effort in the last 10 plus years to organize the public workshops and multiple events to kind of review what has been achieved in the past, and also what's been like event like this? Right? What? What will be the sort of a new focus. One thing that I realized by working

with our generic partners is that you know they always complain that. Oh, you know, this is a very cutting edge. But we don't have internal expertise.

so this can be to my opinion it can be easily accomplished by organizing some educational events. So it's I, I think in in this room, and folks on the line. We're like preaching the choir to each other pretty much right? So you probably need the CEOs of you know, the major generic companies and the clinical developer development folks in the generic companies to be in this room to not to understand fully all the science being conducted. But just to know the value of quantitative modeling and simulation today was, you know, like very, very impressive progress.

But I that that's 1 of my recommendation. That can be done very easily.

Moderator: Okay, thank you. I mean. we actually have done significant outreach in the past with our industry stakeholders. So probably not in this workshop in some other workshops. But we will continue outreaching for sure

Ping Zhao: that that happens for the new drug. Right? So it's a you know, kind of a preaching the choir. So you kind of you can. You can get into the you know, sort of a into the weeds very easily. But one thing I was very impressed by the availability of many of this visual tools that you could take advantage showing people, hey? You know there is a black box. There are tons of equations but you don't really need to understand all these right. But I can show you these tools can generate similar digital twin-ish results that can be convincing enough, totally transforming our way of thinking, the traditional paradigm where clinical study has to be the gold standard. So I think that's the essence of what Dr. Zhao presented the second slide. I think that the essence of this is using modeling simulation combined with a limited number of studies to make an impact.

Moderator: Thank you..

Comment: So I thought there really were remarkable set of presentations today. And so something that was sort of a thread that seemed to come up over and over again is the availability of data to qualify, evaluate, train. So are mechanisms to enhance the organization and access these to data that are generated that would be germane in the public domain. Anything you know, publicly funded information or perhaps even the pre-competitive space, very much like the critical Path Institute speakers had alluded to. And that information is not necessarily limited to just strictly measurements and say physiological parameters.

But even elements of these models that can be shared, and that can be utilized, and maybe even front end, so that people can explore these without having to have really advanced knowledge of sort of the engines underneath. Those are sort of my general observations in that regard. Thank you.

Moderator: Thank you. Actually, that's a very good comment. And that's for you, you cannot actually upon the model sharing the that's why we actually kick off the new initiative on the model master file. We just had the workshop, but a couple of weeks ago. Yeah.

Comment: And you and FDA has been really the forefront of creating tools that are publicly available in in this regard.

Moderator: Many thanks to the GDUFA research program. Any comments from our FDA panel members? I will come to you guys later that you guys just spoke.

Okay, Rebecca.

Rebecca Moody (Biopharm): Hi, yes, I'm Becky Moody from biopharm.

You know what is gonna drive for quantitative ma quantitative modeling. I really think it's the in vitro tools. Your model is only gonna be as good as the data that you put into it.

So I think that we need more research into that and you know, on top of that, we need additional outreach global harmonization. So that people know that they do these tools, that they're going to be accepted, not just by FDA, but by other authorities. Because drugs are not.

you know, manufactured in an isolated system. They're for global use mostly.

Thank you.

Moderator: Thank you, Okay, Ahmed.

Moderator: Yeah. I just have a comment and maybe a question to all panelists. Also, one of the successful point for modeling approach is to mimic the actual scenario as much as we can, right?

So for most of the locally acting generics and drug products. So there is an environmental factor and patient factor. For example, the metamorphosis that's happening at skin surface or and or add the ocular surface. This evaporation that may happen may change dynamics for, or the kinetics for absorption and availability.

So how do you think we can include this, or what advances that we may include in the modeling efforts.

Moderator: Any other comments?

Sivacharan Kollipara: First of all, thank you for this wonderful experience. And it's really great to see all the great thoughts and wonderful initiatives that are coming from.

I echo with the thoughts that the other panelists are mentioning. But what I also believe is that in order to facilitate this. QM. Much more focus needs to be made on advanced routes of for delivery. Let it be ocular or transdermal or inhalation. And as other FDA panelists was saying that the output from the model depends on the inputs that we are giving. So it is important to have in vitro tests which are mimicking the in vivo behavior. That can be aerodynamic particles as distribution in case of inhalation products or incorporation of certain formulation, specific attributes like viscosity or the evaporation rate in in case of transdermal formulations.

what is also important to consider along with the in vitro tests and advanced routes of delivery systems is understanding the physiological aspects. How accurately the models are mimicking the physiology in case of healthy populations as well as in case of diseased populations. When all these things are combined together, the chance of prediction or success of the model, model, the in terms of the output that increases. And that's how I feel that we can facilitate the research in this particular area.

Moderator: Okay, Markham. I think you actually gonna use the mic.

Markham Luke (FDA): So I wanna 1st of all, compliment all the speakers on fantastic talks about models, etc. And I wanna especially thank Jessica for questioning the validity of the tape stripping tape stripping is a primitive model it thinks the skin is a flat surface, and you're really just picking up drug from the surface of the of the skin and the gyrate of the skin as opposed to actually looking at the penetration of drug into skin. So our caution using anything having to do with tape stripping in the context of drugs that penetrate skin, especially for acyclovir that's used for cold sores. It's around perioral. There's and there's no place for tape stripping for that for that kind of drug and the other, you can see some of the fantastic technology that's going into the modeling for the inhalation products. We're very much keen on seeing how that's being developed. And we're looking forward to seeing more of that, how it's being used for a novel propellants and a future products. And there's also interest from the biologics. Space, too, as some of the biologics are being used for with inhalation for larger molecules, etc. So I think there's a lot of promise for how these models are. Simulations are used to develop new drugs, and also to look at a bioequivalence for our for our generic products. Thank you.

Moderator: Thank you, Markham. I see Dr. Andrew Cooper. He has a comment to make.

Andrew Cooper (Viatris): Yes, so it's really interesting to see the discussion today how things are developing on my, a area of interest is inhaled products. So I'm gonna speak specifically to that. It's kind of interesting to see that we know, seeing PSGs with suggestions for including models. So that's developing well, and the FDA, I know are already sponsoring research, looking at validation of models and what I'd really like to see what would really help industry is if you know, the FDA can sponsor research which gets into the public domain. A kind of model validation package for different kind of models, so that we really see what's going to be acceptable for validation.

The other point I'd like to just echo, which I know a couple of people have already made. Is that how you put in vitro data into models.

I think, is sometimes something that gets neglected. So you know, there's obviously a question as to what in vitro data goes in. But often the in vitro data that we're feeding into models is quite complex.

It's not just a single number from a test and just thinking about how you interface the in vitro tests with the models to ensure that you're really capturing the information from the in vitro tests correctly is, is really really important. I'd like to see more work on that and more information in the public domain coming out of that.

Moderator: Thank you, Dr. Cooper. That's very helpful. Now I'm going to transition to Ahmed to ask you for the next question.

Moderator: Thank you, Lucy, so let's move here a little bit to artificial intelligence and machine learning. So, as we have seen in the public comments and the presentations, wonderful presentations today all of us advocate for the application of artificial intelligence and the machine learning in different I would say, phases of generic drug development starting from formulation development characterization, real time release testing manufacturing submission and post surveillance data as well.

So, for example, in post surveillance, artificial intelligence, we have seen in the in the presentation, that it may be used for quality, signaling and real world adverse events like

surveying substitution and supply chain, and even addressing some sorts of scenarios of drug shortages. Right?

So my question to the panelists, which area do you believe is the most urgently in need of research, attention to facilitate development and availability of generic drug product. In regarding to application of artificial intelligence and machine learning, for example, formulation, optimization or formulation, development of generic product bioequivalence prediction and simulation, digital twins, development of release or establishment of real time release testing for drug products and surveillance and drug submission.

So a quick chance open for the panel.

Panelist: Yeah, I think again, we've talked about inhalation. I think it's very clear that one of the major barriers for more products on the market is the clinical endpoint study.

So I think if AI and ML. Can somehow facilitate the replacement of that, so that bioequivalence waiver. I think that's quite urgent, because we do feel we see it on a daily basis, and a lot of companies are a little bit on the sidelines. They say, Yeah, we'll see when that 1st alternative BE approval comes, and then we'll get into the game. So if we're really serious about getting more drugs, inhaled drugs on the market at lower prices then I think we should use every technology we can, including AI and ML to lower that barrier.

Jayanti Das (FDA): Maybe I can add some comments on that thank you so much for all the excellent speakers for the nice presentation. And thank you for the question Ahmed.

So I think, for AI and machine learning application areas digital twin can play a significant role in the coming years, because we always hear that gap between the in vivo predictions versus the in vitro predictions there is always a gap we are struggling with, because there are so many factors involved to have that comprehensive understanding and digital twin can play a critical role here by producing the synthetic data which can encounter countless number of sectors into the model development process. And once we can develop a robust model, I think we can use the real time data for the model validation purposes. So and that can also contribute to the other areas. For example, the formulations where we have to spend a significant amount of time for the formulation development for specific drug products where also digital twin can help us to develop or generate the synthetic data for the model training purposes primarily.

Moderator: So just a follow up to you, Jayanti. So do you think artificial intelligence may be used for reverse engineering, for example, to predict formulation, composition, and to offer some sort of similar formulation of generics.

Jayanti Das: Yes, I believe so. And I think that is one of the factors. People need to take into account, because only that way you can validate your model that whatever you are developing based on the data, it when it can satisfy towards the reverse engineering process. Only that will give you the confidence on the model that it can likely predict in both ways. It's not only predict the dissolution profiles or the bioequivalence, but at the same time you need to make sure that your prediction can also go on the reverse direction, where you can also predict your material attributes or process parameters.

Moderator: So as we see that our main objective, when developing a generic product is to be bioequivalent and efficacious and safe like the RLD or the brand product.

So for this, for the efficacy it includes a lot of factors. And some of these factors we have seen in real data, including variability among the patients. But when we come to the algorithms and mathematics. We barely see this variability there. This variability is inherent part of the PK study, inherent part of clinical bioequivalence study which is coming from human it, which is coming from like the difference or variability inter subject variabilities. So do you think this may be captured by artificial intelligence and machine learning somehow.

Jayanti Das: That's a very good point, actually. And I think the struggle is there. And that's why people are moving towards the hybrid modeling nowadays where you can develop some synthetic data. But as well as you can do some experimental data and have to come to an optimized point where you can get the right or best output from different variability.

Panelist: So if I could jump in for a second, I think a key aspect is, if the measurements are not made, or if we don't understand, are we missing part of the system. AI or machine learning is not necessarily going to tell us about this until you do that experiment, or you see the discordance. In particular. I'm thinking about the presentation on the on, for example, the mucus layers and understanding the interaction with the formulation and that's notwithstanding other variability that might be present in the systems that we've already reasonably well captured. So I'm just throwing it out there. I know that other people that are much, much better experts in this in this area.

Panelist: I think to your point, I don't think the data isn't measured. I think the question had to get to the data because there's millions of CT scans taken every year, maybe every day around the world. So but that data is usually not very well characterized. It's discarded even very quickly, because it's a lot of gigabytes. So it's all about how to be able to access and use the data that is there. And I think that we can solve that problem even a little bit. And we can have a continuous influx of the clinical data that is out there, anyway, into these quantitative medicine approaches. I think that would already solve quite a bit.

Moderator: Yeah, Clare.

Clare Butler: So just to echo what other panelists have said, you know. Thank you very much for the session. It's been really informative. And well done to all the presenters and really fantastic presentations.

So I will just narrow my comments towards inhalation products again. Because that's my area.

And again to echo what others have said. You know predictive models, such as PBPK, there they are only as good as the quality of the in vitro data that's used to inform them, and as such harmonization of the associated methods across industry would be helpful. However, these models are also only as credible as their alignment with in vivo data. And I think, in terms of, say, for example, deposition studies such as you know, in vivo scintigraphy studies.

You know, some funding towards these type of initiatives would be helpful.

Given that if industry were to universally invest in these type of studies. You know, in terms of time and cost.

you know they could spend the same amount of time doing a you know, a PD. Bioequivalent study. So I suppose my point really is that you know, the availability of the in vivo data and funding towards conducting such studies would be would be welcomed from the industry side.

Moderator: Thank you, Claire.

Question: I feel that easier from Dr. De Backer shows a 3D numerical medicine. We also talk about the in virtual model, the CFD, which is the whether they did correct or not. We need to validate that. So basically, I think one very important thing is that the in vitro or in vivo 3D. Data which is make available to be ready for validation of CFD, I think here, basically, I have this here. We have some initial working on this one. I feel that is really the best way. Try to validate, because for drug delivery the most usually the most available is 0D, or one D data, which is just a deposition local deposition, regional deposition and maybe 2D data, which is a scintigraphy data. But now is the 1st 3D. In vitro, which is possible. The question is, how to present that with a 3D. Information, make it available for the CFD community for validation. Scintigraphy, the nuclear medicine is ready. So I think, is, I saw this are quite impressed. That is, it shows here reading, though, it shows the volumetric that ventilation. Or if there is some deposition data that would be excellent. That's my comment.

Moderator: Thank you.

So, moving from artificial intelligence and machine learning. Rebecca.

Rebecca Moody: Oh, sorry. I just wanted to add one additional comment, just building on what everyone else said. One area in particular, where I think that this could be very useful, is in looking at characterization of some of these complex dosage forms that you see with the locally acting products.

And here, you know, I'm not even talking about anything really crazy. But, like, you know, we already predict aqueous solubility, you know. Why can't we go ahead and start predicting the solubility in some of these different vehicles and things like that?

You know, if you look at the multi component mixtures, for example, the theoretical basis for that for tackling solubility, for those, I think, is fully solved. But I suspect we could use machine learning to get maybe 95% of the way there. You know, good enough for what we're trying to do, or at least get us in the ballpark.

So that I think that these also some areas where machine learning would be very useful

Moderator for more complex cases after that, for locally acting still needed.

Rebecca Moody Yeah, absolutely.

Moderator: Yes. So in the same part, I am talking about the complexity of the orally inhaled drug.

The drug availability of site for action is mediated by many processes starting from the device delivery administration parameters, regional deposition interaction with biological components, distribution permeation, mucociliary clearance right? So which of this area do you think will, like the research is needed to substantially increase the usage of orthogonal approaches to support the administration of bioequivalence of generic drugs.

Panelist: I think we have to determine, 1st of all, what are the most important drivers for the outcome that we want to study.

So if you say, Okay, we, we think regional exposure to the drug is the most important thing. Then we kind of have to, I think, making sensitivity, and also see, okay, which parameters are very influential and which one ones are less influential. And then investor research, and the ones that are the key drivers for that. And I think we kind of know it to a certain to a certain extent, and then we can. We can build on that. But I think that's probably because the thing I think we need to avoid they were spending a lot of time, a lot of resources in modeling things that in the end might not matter, simply because we didn't take the time to take a step back and see. Okay, in the grand scheme of things, I can tell you. Very important part is the way the patient uses their inhaler. For instance. We can do evaporation models and particle interactions. But if we don't get the inhalation profiles and right? And when I say right, meaning the digital equivalent of what happens in reality, then it's probably not a very good point of investment. So I think we need to know what is really important before we kinda invest Now.

Moderator: Thank you. Anything from FDA?

Bryan Newman: Yeah, Hi, I, I think Jan touched on that important part. There's obviously lots of complexity with these products. And so the challenge tends to be trying to narrow down what needs to be our focus. So we have in vitro methods that we've put into our own alternative approaches already that we have confidence in and you know we've invested it in silico models. We have the grants with Fluidda to look at the, you know, validation for deposition for imaging. So I think that the challenge is trying to again identify where the actual issue is like. So if there's additional and vitro methods that people want more, you know, studies on or whatnot to focus on. I think that needs to be provided, because certainly I saw lots of presentations on permeability today. So you know, that might be something that we could consider. But again, I think that's the type of input we, we will tend to need because we want to get be able to focus on this. Because, you know, we want to make sure we our resources are going to be focused on the areas that have the biggest impact. And you know, if I just continue with like another tend to focus again, we have the alternative approaches for some of these products, and we tend to focus on using these for formulations that are essentially Q1, Q2 the same.

So I think the next push for this is really trying to see how we can utilize some of these for non. Q1 Q2 formulations. I see that's a you know, particularly a way to help with efficiency and can help with.

When we turn to formulations like with the transition for propellants when you're naturally not going to have that same type of formulation. But the challenges as you could do these bigger changes again, what's the correct type of methods you want to use for this? Is it really appropriate? Do we need to do some type of sensitivity analysis? I think those need to be taken into consideration. But you know, we're certainly open to getting more feedback on this to make sure that you know we're going to where also industry has the most questions.

Moderator: I think. There is a room for one question from the audience if anyone thought

Panelist: to make a make a quick comment. I heard a lot about validation verification. This is a seems to be like a deja vu, you know, from the new drug era. It continued to be there.
I'm getting a bit pessimistic. I'm not against validation, but we have to sort of start to think outside the box. I mean, there are comments on, we're using this in vitro data how to how to make the data useful for model validation. But this way of thinking is a bit linear, right? So we always think, okay, for this new molecular entity. We build the PBPK model, we do some in vitro studies.

We validate a model, or what type of additional data will be needed. But without realizing actually, now, with computation, you're actually building something so impressive that you know this foundation model for AI, like what Jan presented is probably coming from different compounds, different programs. I think that's really powerful.

you know. I really like his cartoon. I don't know him, but I'm not like endorsing anybody in the room, but you know, I totally agree, like before 2016. Right? You. You have a robot with just this limbs, and, you know, like a head. Of course, you know people would be scared of that thing representing the human physiology.

2024, not anymore. I mean, we have to be really ready for the power, the power of data, of information. People keep saying, you know, we don't have enough data. I have conversation with the with Liang on this. It's like, you know, like to do. AI, you need a lot of data. But probably we have more than what we needed. If you look at today's presentation. How many partners working on the CFD models? Right? Then? Probably the next stage is get together and agree on something and just move on right? Because we don't want the perfection to kill the good. As we're saying around that something similar. So that's something I like to stress. Yeah, don't let validation, you know, stall our progress.

Panelist: I have a comment on that.

Thank you so much for bringing a very important point on that. You are very right. We have so many data. But the problem is, there are very less amount of data within the amount of data we are generating. We are actually using those data for real time analysis or getting some real contextual information out from there. So I think that is the important tent we need to be. Consider about that the amount of data we are generating. Sometimes those data lack of proper context, sometimes those data lack of proper connectivity.

For those we cannot utilize that those data at full capacity. So I think that is the challenge we are experiencing nowadays.

And once we develop the model, I think it's not just one time validation. We need to think for continuous learning of that model with the new incoming data in order to ensure that your model is fit for variable factors.

Panelist: Yeah, totally. So that's perfect research question for AI ML, direction, right? So you know, I think that's probably you know everybody in this room together. We will never get there. But maybe computer can help us. Yeah, I just want to leave it there.

Panelist: And I would like to mention one more thing that we, we talk about AI, that capability of AI. But AI also comes with its own set of challenges and limitations. So the data needs to be very good. The data needs to be clean. The data needs to be standardized in order to best utilize the data. So that is, that is very important for AI applications.

Moderator: And when they say also, it is just emerging, I would say, approach just arising. And every day you are getting some new data, and it promises to have better models tomorrow. So it is still an area of research that we need to work on.

So with this we are concluding our session, and let's thank them one more time, all our speakers and all our panelists and thank you for staying with us today.