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Session 2 – Tackling Formulation Sameness and Advancing In Vitro Characterization for Bioequivalence of Complex Generic Products

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Bryan Newman, PhD Lead Pharmacologist, DTP I, ORS, OGD, CDER, FDA
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- **Challenges with Method Standardization for Inhalation and Nasal Drug Products**
  Susan Boc, PhD Pharmacokineticist, DTP I, ORS, OGD, CDER, FDA

- **Biopredictive In Vitro Characterization to Correlate Quality Attributers to In Vivo Performance**
  Hailing Zhang, PhD Division Director, DPQA XII, OPQA II, OPQ, CDER, FDA

- **Advancing In Silico Methods & Understanding the Impact of Compositional Differences on Performance**
  Ross Walenga, PhD Senior Chemical Engineer, DQMM, ORS, OGD, CDER, FDA

- **Research Opportunities to Support Further PSG Development for Orally Inhaled Products**
  Andrew Cooper, PhD Sr. Director, Development for In-Vitro Performance Lead, Viatris Inc.

- **Enhanced PBPK-Based IVIVE Method to Support the Development of Pulmonary Drug Products**
  Maxime Le Merdy, PhD Director, PBPK Research and Collaboration, Simulations Plus

- **Microstructural Techniques for Demonstrating Bioequivalence in Dry Powder Inhalers**
  Nuria Manzano Jurado, BSc Specialist, R&D Pharma Services, Nanopharm

- **Application of Mechanistic PBPK Modeling to Understand Drug Release from PLGA-Based Solid Implants**
  Naresh Mittapelly, PhD Research Scientist II, Certara UK Ltd, United Kingdom

- **The Utility of In Silico Modelling and Substitution Risk for Generic Orally Inhaled Drugs**
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Panel Discussion

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Moderator: Alright, we'll begin our next session entitled "Tackling Formulation Sameness and Advancing In Vitro Characterization for Bioequivalence of Complex Generic Products."

I'm Dr. Brian Newman, lead pharmacologist and team lead for the nasal inhalation products team in the Division of Therapeutic Performance, Office of Research and Standards within OGD. I'll be co-moderating this session with Dr. Ahmed Zidan, senior research pharmacologist in the Division of Product Quality Research VI within the Office of Pharmaceutical Quality and Research.

The session will cover challenges and innovations in demonstrating bioequivalence for complex generics like nasal and inhalation products, complex injectables, and drug-device combination products, focusing on formulation sameness and in vitro characterization. Topics include method standardization, biopredictive and microstructural methods, and in silico modeling. We'll have a total of 8 talks, 3 from FDA and 5 from industry, before a panel discussion. All speaker and panel bios can be found on the GDUFA workshop website.

I'd like to emphasize that the aim of this workshop is to solicit input on research priorities for FY26. We hope the discussion will provide needed input to support this. As a reminder, questions will be held for the panel discussion to ensure we move through the session efficiently. We welcome public comments - please provide these to the public docket. We monitor this, so if there are additional comments that would aid the discussion, we can mention them during the panel discussion.

With that, I'd like to invite our first speaker, Dr. Susan Boc, to give her presentation. She's joining us virtually. She is a pharmacokineticist in the Division of Therapeutic Performance, Office of Research and Standards in OGD. Her presentation title is "Challenges with Method Standardization for Inhalation and Nasal Drug Products." Let's welcome Susan.

Susan Boc (FDA)
Thank you, Brian. Good afternoon. This talk focuses on the challenges related to method standardization for inhalation and nasal drug products.

[Disclaimer slide shown]

Recently recommended and revised product-specific guidances (PSGs) on locally acting inhalation and nasal drug products have focused on providing an additional option for demonstrating bioequivalence of test products to the reference standard. Generally, an option-based approach has been provided in which Option 1 includes recommendations for formulation sameness and an alternative approach to the comparative clinical endpoint BE study. Option 2 is a traditional weight-of-evidence approach that includes accepting studies.

Some studies that may be recommended as part of the alternative approach include in vitro BE studies, in vivo BE studies, comparative characterization studies, and optional studies as shown

in this table, with studies for inhalation products listed on the left and studies for nasal drug products on the right.

The recommendations provided in the PSGs are kept somewhat general since there are still many ongoing questions related to the various alternative studies. This presentation will touch on the ongoing challenges related to in vitro BE studies, specifically realistic aerodynamic particle size distribution (APSD), dissolution studies, and comparative characterization studies.

Dissolution studies can provide understanding of how the active pharmaceutical ingredients may dissolve and become available for absorption. This is a critical aspect that influences the bioavailability of the API at the site of action. This is particularly true for poorly soluble or dissolution-limited APIs. Therefore, depending on the API of the drug product, BE recommendations for inhalation and nasal drug products may include dissolution as an alternative approach study.

General recommendations include that an appropriate apparatus should be used to determine dissolution measurements using a developed and validated method to support its sensitivity in detecting differences in performance between test product and reference standard. Bioequivalence is based on comparative analysis of dissolution profiles using an appropriate statistical method.

The ongoing challenges related to dissolution studies include the standardization of sample collection methods such as size-fractionated samples, representative lung samples, lung-deposited doses, or total doses, and also the choice of dissolution apparatus, including considerations for selection of apparatus for dissolution. Some example apparatuses that have been used for dissolution measurements of inhalation and nasal drug products, as found in the literature, are shown in the figure, which includes USP and novel apparatuses.

Other ongoing challenges include whether to develop a discriminatory and/or biopredictive method and the use of additional statistical methods that would be appropriate to determine bioequivalence.

For inhalation drug products, the realistic APSD study provides assurance of comparable total lung deposition and some assurance of comparable regional lung deposition based on similarity in APSD for more clinically relevant conditions and considerations of patient variability. An example realistic APSD test setup is shown in the top figure, which includes a mouth-throat model and a breath simulator used to generate the selected breathing profile, examples of which are shown in the bottom figure.

General recommendations include performing studies using breathing profiles that are representative of the entire patient population. Bioequivalence is based on population bioequivalence or other appropriate statistical analysis of impactor size mass for each mouth-throat model and breathing profile combination.

The ongoing challenges related to realistic APSD studies include the selection of inhalation profiles and relevance of the dosage form of the drug product on the profile selection, considerations for mass balance and methods to reduce variability, correlations of APSD parameters with in vivo performance, as well as identifying additional statistical methods appropriate to determine bioequivalence.

For inhalation drug products, the particle morphology of the residual drug particles once deposited in the lungs may impact product characteristics that affect bioavailability at the site of action. Thus, comparative characterization of the test product with the reference standard may be included as an alternative approach study.

General recommendations for comparative physical-chemical characterization studies are minimal and may include characterization of the polymorphic form of the drug substance, the particle morphology of the emitted dose, and an evaluation of the crystalline/amorphous content of the test formulation and reference standard.

Ongoing challenges related to comparative characterization studies include identifying and selecting the appropriate techniques for characterization, sample collection and preparation, clinical relevance of the physical-chemical properties to performance, and quantitative evaluation and determining appropriate statistical analysis.

For inhalation drug products, FDA has several current research grants and contracts that are working to address some of these challenges. These include research to study the use of more biorelevant dissolution apparatus. The objective of this research is to evaluate the discriminative power of the proprietary Dissolvit system that was developed to provide a more physiologically relevant in vitro dissolution test system.

Studies with realistic mouth-throat models that can facilitate study optimization and reduce potential for method variability are being explored, as well as research using various imaging techniques that can aid comparative characterization study method optimization, method development, and understanding of relevance to clinical performance. Imaging techniques being studied in these research projects include scanning electron microscopy (SEM), focused ion beam high-speed microscopic imaging, optical coherence tomography, optical photothermal infrared spectroscopy, and atomic force microscopy infrared spectroscopy.

FDA has also completed research related to nasal spray drug products that resulted in the development of adult and pediatric in vitro nasal models used to evaluate regional deposition with typical nasal spray device designs.

Potential remaining research gaps include the use of in vitro models to evaluate nasal spray products with more complex device designs or location for deposition and implementation of in vitro models to support bioequivalence assessment.

In summary, there are still ongoing challenges regarding specific recommendations for alternative studies provided in product-specific guidances for demonstrating bioequivalence of test inhalation and nasal drug products to the reference standards. These include:

1. Dissolution challenges related to method development and statistical analysis
2. Realistic APSD challenges related to breathing profiles, variability in data correlation to in vivo performance, and additional methods for statistical analysis
3. Comparative characterization challenges related to methods, sample collection, discriminatory ability, qualitative and quantitative analysis, and relevance to in vivo performance

There's ongoing and recently completed research in these areas; however, potential gaps still exist.

With that, I'd like to acknowledge my colleagues in ORS, OGD, and OPQ. Thank you.

Moderator:
Alright. Thank you, Susan. I'd like to introduce our next speaker, Dr. Hailing Zhang. She's the division director in the Division of Product Quality Assessment XXII within OPQ. Her presentation title is "Biopredictive In Vitro Characterization to Correlate Quality Attributes to In Vivo Performance."

Hailing Zhang (FDA)
Good afternoon everyone in the room and hello to everyone joining us online. Thank you, Brian. Today, it's my great pleasure to have this opportunity to discuss this important topic with you: biopredictive in vitro characterization.

[Standard disclaimer shown]

In OPQ, we believe that everyone deserves confidence in their next dose of medicine and that pharmaceutical quality assures the availability, safety, and efficacy of every dose. These two statements from OPQ are particularly relevant to what I will discuss here today with you.

I'd like to start my presentation with the definition of biopharmaceutics. Biopharmaceutics examines the interrelationship of the physical and chemical properties of a drug, the dosage form, and the route of administration on bioavailability, which further determines the onset, duration, and intensity of drug action.

Biopharmaceutics is mainly concerned about the link between quality attributes and in vivo performance, and it is all about patient-centric quality standards. The goal of establishing patient-centric quality of drug products is to ensure that the drug product can consistently deliver the performance as described on the label in terms of safety and efficacy, not only over the shelf life from batch to batch but also for different manufacturers in the case of generics.

Another equally important aspect of establishing patient-centric quality is to ensure the drug product is available to our patients when needed. Patient-centric quality standards can be defined as a set of criteria and acceptance ranges to which drug products should conform in order to deliver the therapeutic benefit indicated in the label. Patient-centric quality standards can increase flexibility within the pharmaceutical manufacturing sector while maintaining quality by establishing acceptance criteria based on clinical performance instead of process capability or manufacturing process control.

Patient-centric quality standards avoid under- or over-discriminating specifications, both of which are contrary to patient needs and interests. However, there are many obstacles to establishing patient-centric quality standards for a drug product. This is because the link between individual quality attributes and in vivo performance is often missing or weak. Quality control tests often lack biorelevance. Biorelevant tests may not be biopredictive. Also, animal study results often cannot predict human clinical performance. Furthermore, clinical bioavailability studies to evaluate every critical bioavailability attribute are impractical and expensive.

The critical bioavailability attributes (CBAs) are the formulation or process attributes that are expected to critically impact the bioavailability of a drug product. For locally acting complex drug products such as oral inhalation products, understanding and defining patient-centric quality standards is even more challenging.

First of all, it is challenging to identify clinically relevant quality attributes. Let's use albuterol sulfate aerosol inhalation as an example. For a Q1/Q2 formulation, the product-specific guidance recommended six in vitro tests: single actuation content (SAC), aerodynamic particle size distribution (APSD), spray pattern, plume geometry, priming and re-priming, and finally realistic APSD. Among these six tests, it is very hard to tease out which ones are directly correlated to the clinical performance. In other words, which ones are truly clinically relevant?

The second challenge comes to the characterization methods. When a physical-chemical property is identified to be correlated directly to its clinical performance, what method should be used to characterize it and how should we interpret the data? For example, what are the proper statistical analysis methods that should be used to establish the clinically relevant acceptance range for those physical-chemical properties?

Another obstacle for locally acting complex drug products is that we do not have many meaningful in vivo data to help us establish an in vitro-in vivo link. I guess because of all these reasons, the research of IVIVC or IVIVR for those drug products is very limited.

Given all the challenges I just discussed, biopredictive in vitro characterization of these complex drug products is critically important to establish patient-centric quality standards. Biopredictive in vitro characterization refers to laboratory techniques and methods designed to simulate and predict the behavior of pharmaceutical compounds in the human body.

Biopredictive in vitro characterization should be developed and validated with the goal to correlate the individual test data to the in vivo performance. So we're looking for some type of IVIVC or in some cases IVIVR between the biopredictive in vitro characterization data and in vivo data.

However, we recognize that most biopredictive in vitro characterization methods are too complex and most likely will not be suitable to be used as quality control tests. Therefore, we need to develop simpler and more robust quality control tests.

If we could develop relevant quality control tests with acceptance criteria that correlate to the biopredictive in vitro characterization, then we are confident that the QC test is not only reliable to ensure the drug product delivers the therapeutic benefit indicated in the label throughout the shelf life and from batch to batch, but it also can be utilized to manage post-approval changes and in some cases can be used to develop generic products. In this case, we can achieve the goal of establishing patient-centric quality standards.

I'm going to use an example here. Pressurized metered-dose inhaler or pMDI as an example to further this idea, meanwhile to highlight the challenges in this field. Albuterol sulfate aerosol inhalation I mentioned a moment ago is a pMDI.

We all understand that aerodynamic particle size distribution after actuation determines how much drug is delivered to which part of the airway. In other words, it determines the local deposition of the drug, which in turn is directly correlated to its clinical performance. But then how to measure aerodynamic particle size distribution?

A moment ago, Dr. Susan Boc mentioned realistic APSD in her presentation. Realistic APSD is a biorelevant method to characterize the aerodynamic particle size distribution because it can mimic more clinically relevant conditions and it also can take patient variability into consideration.

However, in order to use the realistic APSD data to predict clinical performance, we still need to link the in vitro data from the realistic APSD to local deposition because the lung local deposition determines the local bioavailability of the drug and hence the efficacy. However, this could be very challenging. Susan already mentioned the challenges of method development and data interpretation in her presentation.

Furthermore, we also do not have high-quality in vivo lung deposition data to directly establish IVIVC or IVIVR.

Let's take a step back to discuss APSD. APSD can be determined by a cascade impaction method described in USP <601>. It is used as a quality test to judge product quality and performance. However, the acceptance criteria are mostly decided by the clinical or registration data batches and have little to do with the clinical performance. Therefore, it is possible that the acceptance criteria are too stringent and lack flexibility.

However, if we can correlate the APSD acceptance criteria to the results of a biopredictive realistic APSD, then the quality test APSD is also linked to the clinical performance. In this way, we may be able to establish a safe space for the APSD acceptance criteria which is correlated to the clinical performance, which may offer more flexibility. However, such research to link this to realistic APSD is non-existent.

So I hope you will agree with me that research gaps for biopredictive in vitro characterization are obvious. Research is needed to correlate in vitro characterization to clinical performance so the in vitro test is truly biopredictive. Research is also needed to establish clinically relevant safe space for critical bioavailability attributes with the goal of establishing patient-centric quality standards.

I believe research opportunities exist for developing and validating biorelevant models as well as in silico modeling and simulation approaches in this field. I think our next speaker, Dr. Ross Walenga, will be discussing in silico methods further in his presentation.

With that, I'd like to acknowledge my colleagues from OPQ and OGD. Thank you for your time and attention.

Moderator:
Thanks Hailing for the interesting presentation. Our next talk will be given by Dr. Ross Walenga. He's a senior chemical engineer in the Division of Quantitative Methods and Modeling within ORS. His talk is titled "Advancing In Silico Methods and Understanding the Impact of Compositional Differences on Performance." Let's welcome Ross.

Ross Walenga (FDA)
Alright. Thank you for the introduction. I'm pleased to be speaking here today.

[Standard disclaimer shown]

I'll be speaking about compositional differences of non-orally administered drug products. Just a quick definition of what I mean by non-orally administered drug products: This includes buccal, injectable, intrauterine, nasal, orally inhaled, ophthalmic, otic, rectal, topical, and vaginal drug products.

In some instances, Q1/Q2 sameness may be required or recommended. It can be required by regulation for products such as injectables, ophthalmic, and otic drug products. For products where there may be non-conventional BE approaches, for example, in vitro totality of evidence or in vitro-in vivo combination approach, it may be recommended. However, there may be some instances where there are benefits to having a non-Q1/Q2 formulation. For example, there may be patent protections that make it difficult to have a Q1/Q2 formulation, complex formulations where it's just challenging to come up with a formulation that's the same, or even supply issues.

Mechanistic modeling is one tool that we can use for understanding the impact of these compositional differences. It can facilitate drug development and/or approval for non-Q1/Q2 formulations and can help us better understand the potential impact of compositional differences on product performance.

I'll be speaking specifically about physiologically based pharmacokinetics (PBPK) models or computational fluid dynamics (CFD) models, and the effects of Q1/Q2 differences and even Q3 differences, which will be physical-chemical characteristics. If they're to be considered for models for products such as those applied to the skin or orally inhaled drug products, they may need to account for processes such as evaporation and condensation, spray formation, and changes in permeation and dissolution due to excipients.

I'm going to walk through three different product areas and show the kind of challenges that we see in these areas, the currently funded research, and where we see potential research gaps as a means of stimulating the conversation.

For topical products applied on the skin, historically we've recommended comparative clinical endpoint or pharmacodynamic studies. But currently, we have supported GDUFA research, streamlined our approaches, and we now have in vitro characterization and performance test recommendations in many cases.

One problem, though, is that if you have products with compositional differences, you have potential metamorphosis on the skin, and this can be dictated by thermodynamic activity of the active pharmaceutical ingredient, which then can affect the way that the product is absorbed.

One potential solution is to look at in vitro approaches along with in silico approaches that can help better understand the impact of this metamorphosis. So we're looking for mechanistic PBPK models that can understand metamorphosis phenomena after you apply the product on the skin as well as the impact of inactive ingredients on API thermodynamic activity.

We have several currently funded awards right now. The top two relate to better understanding thermodynamic and functional characteristics of topical formulations. The third one is about in vitro testing to support BE determination when you have formulation differences. The fourth is for the role of excipients and excipient substitution in topical semi-solids. The fifth is for further development of an existing dermal PBPK model, and the sixth is a toolbox for further developing the capability of these dermal PBPK models to consider metamorphosis.

Where we see the potential remaining research gaps is to first predict simultaneous permeation of the API and inactive ingredients and potential mechanism-based interactions, to understand the vehicle loss and its impact on API formulation (because while metamorphosis is happening, the vehicle is evaporating dynamically), so we want to better understand this process. And lastly, understand the impact of drug product handling such as rubbing on API permeation.

Switching to locally acting metered dose inhalers (MDIs) and next-generation propellants: We have a new batch of revised or new product-specific guidances beginning in February of last year that have two options for bioequivalence instead of one, as the two previous speakers mentioned. For option two, this does allow for non-Q1/Q2 differences, but it still includes recommendations for comparative clinical endpoint or pharmacodynamic study.

One problem we're seeing is that we have a need for non-Q1/Q2 formulations because we have this transition to next-generation propellants. One potential solution is to use modeling as one tool among many, including CFD or semi-empirical methods for regional deposition predictions or PBPK models for PK predictions to support product development and predict the impact of device and formulation changes. This can provide support for addressing the uncertainty of non-Q1/Q2 formulations and can potentially facilitate the option one approach which does not include a comparative clinical endpoint study, even with the change in propellant.

We also have several currently funded awards here. The top award is for CFD modeling of MDIs. The second one is for better understanding the impact of switching to a next-generation propellant. The third one is CFD modeling for dry powder inhalers and also using a machine learning method to accelerate that process. The fourth one is for conducting an in vivo imaging study to develop a validation toolset for CFD modeling. The fifth is for collection of protein tissue expression data to enhance our PBPK models. And the sixth is to collect permeation data to also enhance PBPK models and to further develop an existing PBPK model.

Among the potential remaining research gaps I mentioned, the validation toolset for in vivo imaging - these are typically for only one active ingredient, but there really haven't been methods developed yet for two active ingredients. Also, Michaelis-Menten kinetics data for all the protein tissue expression data that we have now. And dissolution modeling has advanced to a certain point, but we believe that this could still be further improved.

Lastly, I'd like to speak about long-acting implant and injectable formulations, specifically PLGA-based formulations. These are products that do require Q1/Q2 assessment, but these are still complicated to understand in terms of the composition, because the composition of PLGA polymers can affect product performance and is heavily reliant on the properties of these polymers.

The problem here is that the current Q1/Q2 assessment requires comparative physical-chemical data relating to these PLGA polymers. We want to further understand how impacted differences in these characteristics translate to critical quality attributes and then further translate to in vivo performance. Also, there are challenges with the PK studies in this area because you can have very long duration PK studies, which can lead to low subject recruitment and other problems. As a result, we believe that this is why we do not have too many generics on the market right now.

One potential solution is to use mechanistic modeling of these products to better understand the in vivo release mechanism and to then use this to justify why differences in characteristics may not impact in vivo performance. To advance this, we're proposing to use virtual bioequivalence methods or in vitro-in vivo correlation methods.

We have two currently funded awards here, one for development of a mechanistic IVIVC for PLGA implants and the second for a virtual BE platform. The gaps we see here are developing a mechanistic model that can account for critical formulation attributes such as PLGA monomer ratio, molecular weight of PLGA, polymer end-cap, drug loading, and porosity, and to use these to better understand in vitro and in vivo drug release mechanistically.

A few conclusions:
1. There are instances where a non-Q1/Q2 formulation may be advantageous for non-orally administered drug products.
2. Mechanistic modeling methods such as PBPK and CFD may facilitate drug development and/or approval for these products.
3. Our research has been funded to support use of mechanistic modeling for topical, MDI, and PLGA implant products and injectable products.
4. I identified some potential research gaps that may be important to focus on for future GDUFA-funded research.

Your job as the audience, and especially from industry, is to think about these gaps and to think if these apply or if there are other ones that you're maybe thinking of.

I have a few acknowledgments for my coworkers, especially Drs. Alam and Tsakalozou who helped with development of these slides. And I've got the references for your further reading later on.

Moderator:
OK. Thanks Ross. So for our first industry talk, please welcome Dr. Andrew Cooper. He's a senior director and in vitro performance lead at Viatris. His presentation will be "Research Opportunities to Support Further PSG Developments for Orally Inhaled Products."

Andrew Cooper (Viatris)
Thank you for the opportunity to speak. I think my title has already been provided to you, so I'll move swiftly on, and in fact, some of the contents of this slide have already been alluded to by all the previous speakers.

But I guess the way I would describe what's happening for inhaled products is a paradigm shift, and it's a paradigm shift that's taken an awful lot of GDUFA-funded research to implement. That paradigm shift has seen us move from historical guidances with a clinical endpoint study to now, where we have in some guidances as they come through, two options.

The elements of that have already been alluded to by previous speakers. But I guess from an industry perspective, this shift provides a tremendous opportunity for more efficient development of generic inhaled products because the clinical endpoint studies are difficult to do and expensive. But it also raises some challenges, and those have already been discussed to some degree.

We have additional in vitro studies, and whereas the more traditional in vitro studies are based on QC tests, these new in vitro studies of realistic APSD, dissolution, and comparative characterization are much more based on developmental tests that people have been working on for a number of years. And so there are a number of challenges relating to the implementation and execution of those tests to generate bioequivalence outcomes.

The other challenge is that with this enhanced package of data that we see in option one where we've got additional in vitro tests and also the introduction of charcoal block studies with PK, we're generating a much more complex set of data. And so the challenge really is to understand how these tests work together to predict local equivalence.

And of course, the other changes that we're seeing - computational modeling recommended as an option to support BE - and it's also a challenge to know exactly how that will work out.

So I'm going to talk about a couple of examples of some of the topics under discussion where there may be scope for further research. The first thing I'm going to talk about is dissolution, where there's a tremendous diversity of approaches that people have used in a research sense, and how do we translate those into tests which are maybe a bit more standardized and suitable for BE?

I'm going to start just by introducing you to an approach to dissolution of inhaled products that we've used in our lab. And I'll go on to explain why I need to introduce this in a moment. But essentially within our own lab, we've used standard apparatus to do both the collection of the dose and the dissolution, although we've used the apparatus in a slightly non-standard way.

What we've done is to collect the dose in a cascade impactor by liquid impingement in a non-soluble medium. The advantage of doing that is that we avoid some of the agglomeration that results if you try and collect powder in a cascade impactor for dissolution testing. So the liquid impingement helps to maintain dispersion of the particles.

Having done that, we then quantitatively transfer the collected powder into a standard USP 2 paddle apparatus. We add a solubilizing medium to the vessels and then we carry out the dissolution test.

I'll just show you one piece of method development data that we regard as rather important for this kind of method, which is to show that the dissolution rate is not dependent on the mass deposited. What we've got on the left here are dissolution curves that have come from putting one dose and then two doses into the apparatus, and you see a nice proportionality there. When you convert that data to percent dissolved as on the right-hand side, you get a nice overlay of the curve. That's what we like to see in a dissolution method because it suggests that you're not artifactually forming agglomerates as you collect more powder in the apparatus.

Now here we come to the really interesting slide. What we've done here is an experiment where we've compared dose collection methods, but we've used exactly the same dissolution media and USP 2 apparatus to do the dissolution, and we've used a set of 6 product variants that were engineered deliberately to have differing dissolution characteristics. We've put those same 6 product variants through three different ways of collecting the dose.

So there's our liquid impingement method described on the previous slides, and then two methods that others might be more familiar with. We've collected the dose on a filter basically at the end of an oropharyngeal cast throat. And then we've also used the UniDose apparatus, which was a product of GDUFA-funded research, and this is proprietary to Nanopharm, again, to collect the dose.

What we see is that we actually get quite similar dissolution rates between the three apparatuses or three methods of dose collection, but more importantly, what we see is extremely similar discrimination between these three formulations. What this shows is that yes, there's a diversity of approaches, but you can actually get the same results at the end of it. And there's similar data in the literature where people have actually looked at two different types of dissolution apparatus.

This is from work done by Günter Hochhaus' Group at the University of Florida, again, GDUFA-funded research, where this time the dose collection was consistent and then they've put the collected dose into two very different dissolution systems, the USP paddle apparatus like what we've used and then also the Transwell® system, which is a small volume system with a membrane.

Again, what we're seeing is that between three different formulations with differing dissolution rates, at least in a rank order sense, we see similar discrimination even though we've used very different apparatus.

So what does that lead me to think about the concept of standardizing the sort of non-standard apparatus that's often used for dissolution? Well, I think there is definitely scope for standardizing some of the apparatus that's used particularly to get more consistency in approach and execution. And so if we've got particularly filter dose collection setups that have proven ability to avoid mass loading effects, it would be really good to see more of those standardized and made commercially available, and that could be an area where there could be more research.

But I think as we look to standardize, we do actually need to maintain diversity of available approaches because different methods may be optimized to show similar discrimination and different approaches may be required for different applications depending on the drug solubility, the dose, and the formulation characteristics.

Next, I'm going to talk about something that's more related to my second point about understanding how the tests come together. I'm going to switch actually to talking about the pharmacokinetic data that we're now generating, particularly now that for orally absorbed drugs, we're blocking the oral absorption with charcoal, so we're getting a much better sense of the absorption through the lung.

I'm drawing here on a recent paper from the PQRI group who were working on the inhalation biopharmaceutics classification system - a very nice paper. I certainly recommend anyone who hasn't read it to read it. What they've done is to look at the sensitivity of systemic BE differences and factors affecting the local bioavailability of orally inhaled products.

The key things really in terms of local bioavailability are: What dose is in the lung? Where is it deposited in the lung? And then how fast is it dissolved? What they've looked at for different classes of drugs according to their solubility and permeability is where you'd expect to see the sensitivities in the PK data that's really telling you about local availability.

This caused me to go and have a look in the literature and also in our own data to see what evidence there is to actually support this kind of theoretical analysis. Starting in the literature again, GDUFA-funded work from the University of Florida and others where a study was done that was specifically designed to look at the sensitivity of PK to regional deposition, looking at fluticasone propionate DPI variants.

This study involved three FP formulations that differed in their APSD, and it had the intent to investigate the sensitivity of PK to regional deposition. I think it's acknowledged that this study was difficult to interpret because the regional deposition effects were somewhat confounded by differences in the lung dose and dissolution rate in the formulations. But more recently, there was a population PK analysis published that helped to pull apart what was actually happening in

that PK data and supported the hypothesis that PK was sensitive to differences in both the regional deposition and the dissolution rate between formulations.

Also within our own data archives, I had a look at data we had for salmeterol, which is a Class 3 iBCS active. This is not from designed experiments. This is kind of a data mining exercise where I've looked at some early formulation product development PK studies that we did where we did variations in the product, but they weren't designed to achieve differences in PK due to regional deposition.

Nevertheless, within the data, what we see is data that lines up with what the iBCS group predicted we'd see in PK. So first on the left, as kind of a benchmark for this, what we're seeing is an apparent relationship between the total exposure (the AUC) in the PK and the fine particle mass from cascade impactor, which we would expect to have some prediction ability for lung dose. We see a reasonable relationship there.

And then on the right-hand side, which is for me the really interesting bit, is that if we then look at the in vivo absorption rate, which is reflected in the ratio between the Cmax and the AUC, and how that varies apparently with the MMAD in the APSD, which we expect to be predictive of regional deposition, what the theory says is that essentially the finer aerosols should get deeper in the lung, where there's greater surface area, and for a permeability-limited drug like salmeterol, we should therefore see a higher absorption rate with a smaller MMAD, and that is what we see in these data. Now, as I said, this is not a designed experiment. It wasn't PK with charcoal block, so it's possible that oral absorption influenced the outcome to some degree, but nevertheless I can say that the data is consistent with the expectations from the iBCS group.

And so that leads me to think that there is scope to leverage this charcoal block PK data to help us assess regional deposition, because the limited body of existing data appears to be consistent with the predicted sensitivity of PK to regional deposition, at least for one Class 2 molecule and one Class 3 molecule. And of course by using charcoal block we are making sure that the PK is fully reflective of the lung deposited fraction.

And so I think there is scope for further well-designed studies where we look at product variants that can explore that relationship between PK and regional deposition, and that should help us to increase our understanding of the significance of PK together with the in vitro results within the weight of evidence supporting local bioequivalence in the new paradigm.

And so to conclude, first of all the new option 1 BE paradigm creates a bit of an exciting time with new opportunities for science-based approval of generic inhaled products without the need for costly clinical endpoint studies. However, several new and technically complex in vitro tests are involved, which are previously unprecedented in OIP quality assessment. Research into improved standardization of these novel in vitro test equipment and approaches may improve our consistency of approach and execution, but the flexibility to use different approaches for different products must be maintained.

And finally, the inclusion of charcoal block studies provides an increased opportunity to use PK to support local equivalence of regional deposition, but further research may be required to underpin this understanding.

Moderator:

Alright, thanks Andrew. For our next talk, this will be given by Dr. Maxime Le Merdy. He's a director for the PBPK Research and Collaboration group at Simulations Plus. The title of this talk will be "Enhanced PBPK-Based IVIVE Method to Support the Development of Pulmonary Drug Products."

Maxime Le Merdy (Simulation Plus)
Thanks, Brian, and thank you everybody for joining this talk.

So I'd just like to go back to the numbers of the disease actually being treated by this drug product. Asthma represents around 25 million patients in the US as of 2021, and for COPD it's about 10% of the US population being affected. So all of the things we are talking about today around these orally inhaled drug products are actually for millions and millions of people in the US. So FDA's mission to make this rather accessible for a very large number of patient population within the US, and also you guys are leading development globally. So what we present here today affects patients all around the world.

And just to go back, I think it's been introduced in Ross's previous talk around how the absorption occurs for orally inhaled drug products. We have like 3 phases. Phase #1 happens in a couple of milliseconds. It's the deposition - where the drug is going and how much is actually going to settle in different locations. So that's a couple of milliseconds.

Then, in a matter of minutes, we have the dissolution. How the API that is administered as particles actually dissolves into the lung fluids. And finally, once the drug is dissolved in the lung fluids, it can actually penetrate across the lung epithelium and reach the lung tissues, and then the systemic circulation.

So with that in mind, one thing we need to remember and understand is it's only by understanding the complex relationship between those 3 phases - the deposition, the dissolution and absorption/permeation - that we can actually get a clear idea of the local and systemic PK profiles and how this understanding is mandatory for both regulatory assessment and development of generic drug products as well as for new orally inhaled products.

Which brings us to the challenge of actually predicting this local and systemic human exposure. It's difficult because understanding, as we saw in the previous discussion, deposition and dissolution is challenging using in vitro and/or in vivo and/or in silico studies.

So what are the solutions that at Simulations Plus we've worked with in partnership with the FDA is to use PBPK models. We've talked about PBPK - Ross introduced the concept. You can see on the right part of the slide here the initial structure of the lung-specific PBPK models. And one advantage of this model approach compared to others is that it mechanistically integrates the deposition, the dissolution and the permeability.

So you can actually use this model to do in silico experimentation and see what the impact of one of these phases has on the others and what could be the resulting local and systemic exposure. So to go back to Ross's presentation, you can modify because we know the formulation has slightly different deposition and directly test the impact between a test and the reference product.

However, the challenge within the challenge is to parameterize the PBPK model. We don't really have a clear path forward. We knew how to, you know, do some of it. But it was pretty far from having perfect predictions.

So a couple of years ago, us, in partnership with University of Florida, we've been lucky to be granted this project in partnership with the FDA to evaluate the use of in vitro lung cell permeability assays to support PBPK model parameterization.

We started with that PBPK model that divides the lung into like 4 spaces: the extrathoracic, bronchial, and alveolar, and all of these tissues were single tissue layers. So we just had one block representing the tissue and the drug would go from the lung space to the tissue and then be absorbed into the systemic circulation.

The first task that we have done is to modify and improve the structure and you can see the final structure we have on the right now. So much more complex model. And what we've done is for the extrathoracic, the thoracic and the bronchial tissues, we've divided them into different subsections. So we have the epithelium, we have the lamina propria, the smooth muscle, and the submucosa.

So now the model actually represents a real human physiology for the lung tissues. You can see on the screen that for the alveolar we have a different structure because we have two types of epitheliums and same we have integrated this in the model.

More complex model is not always the best solution because it means much more parameters to get. So we've worked with our engineers to find some ways in order to look at how to parameterize that PBPK model. Let's go back to those 3 phases and for deposition, we can use the combinations of in vivo like scintigraphy data, in vitro or in silico like CFD models, to get an idea about the deposition.

For the dissolution as referred to in the previous talk, we can use a combination of in silico and in vitro studies to parameterize this aspect. And for permeability, you know in a similar fashion as is done for oral drug products with Caco-2 and MDCK, we can use in vitro cell-based systems and this is where the collaboration with industry really takes place. They've been generating those new in vitro assays using multiple cell lines for multiple drugs already providing us with a huge set of information in both healthy and patient lung tissues.

So the first case study I'd like to talk about is tobramycin. For tobramycin, for the deposition, we used scintigraphy data. For the dissolution, it was a combination of measured particle size and the solubility predicted using in silico models. And for the permeability we've used in vitro data obtained from University of Florida.

By combining those in vivo, in vitro, in silico information, and informing the PBPK model, we're able to make those pure predictions, so there is no optimization of any kind here. It's really a pure bottom-up prediction and you can see the model is doing a really good job at describing the observed data.

The blue line obtained using the parameter measured in Calu-3 cells, or the one that give us the best overall AUC and Cmax. But we can see that using other cell lines like the mucin we get a very good shape of the profile. So without any optimization, using the new structure we're able to do a complete bottom-up prediction and we could make couple of tweakings to improve. But it's overall really good.

Interestingly, we wanted to see whether that work was actually, you know, making all of the change to the PBPK model make sense. So we went back to that previous version of the model

and use the same approach and you can see that by using a simple model and inform with the same set of in vitro data we get the results on the right which are really bad predictions of the data.

So it's not just, you know, we talk about complexity in the in vitro or in vivo data. It's also complexity of the model that has to be integrated to have that full in vitro-in silico approach to support BE evaluation and also new drugs.

Next case for fluticasone propionate. In this case, we only used in vitro data to inform the model. For the deposition, we use next generation impactor measurement. For the dissolution, it was a USP paddle dissolution test and for permeability once again the results obtained from University of Florida.

In a similar fashion, using the new structure, the PBPK model we get really good bottom-up prediction of the data and the results. Here using the three cell lines are somewhat similar. Same as the case study before, although it's not as significant. We also get a much better prediction using the new model structure compared to the older one.

So to conclude, we have as part of this project, developed a really improved structure of the PBPK model that is much more complex, but actually better reflects the human physiology and also animals. And using this model we get overall better predictions. Bottom-up predictions of the in vivo data in human.

For the tobramycin case study using the Calu-3 cell lines for the permeability assays help us to get the best predictions. For fluticasone, it was the NCIH-441 that worked best. So there is still some unknowns in terms of which cell lines, which assay really is going to help us. At the end, you know to have a final workflow, maybe now we should probably test multiple of them.

But we are working on more compounds. We've in collaboration with the FDA. We have been presenting more case studies to the team and we hope that by the end of the project we'll be able to have more guidance and published final guidance on how to parameterize the PBPK model.

So with that, I would just like to thank the team at FDA, especially Ross and Steven Chopski, and in Florida, Dr. Rodrigo Cristofoletti. At Simulations Plus, my colleague Jim Mullin that has been doing most of the work I'm presenting today. Thank you very much.

Moderator:
Alright, thanks, Maxime. So our next speaker will be Nuria Jurado. She's a specialist for R&D, Pharma Services at Nanopharm. Her talk will be "Microstructural Techniques for Demonstrating Bioequivalence in Dry Powder Inhalers."

Nuria Jurado (Nanopharm)
Thank you, Brian for the introduction. Hi everyone.

As some previous speakers explained already, some product-specific guidance documents have recently been updated to introduce the concept of Q3 microstructural equivalence and the aim of this is to address scientifically valid measurements intended to reflect the rate and extent to which an active becomes available at the site of action. So the extent is about the amount of drug and to address the rate, we need to look at the release or dissolution of the material under study.

So just to summarize, we know what Q1 similarity is: same components. We have Q2 similarity: same components in the same concentration. And then we have Q3: same components in the same concentration with the same arrangement of matter.

So the Q3 approach was successful in transdermal, particularly in the topical area where we even have guidance on how to validate release methods. It was successful in nasal with Nasonex and also in locally acting gastrointestinal products with limited systemic absorption. Now more recently as I was saying in the inhalation field, some PSGs have been updated to introduce these alternative approaches, particularly pMDIs, but if we focus on DPIs now for a minute when we are creating a powder mixture, unfortunately, we don't attain thermodynamic equilibrium.

This means that the aggregation state of the formulation is going to be really dependent on the material properties as well as the processing conditions. Now essentially, the energy that we introduce into the process as well as the interfacial free energy of the drug particles could alter the aggregation state of our formulation. And this is why studying the aggregation state of DPI formulations can help us to understand and address differences between formulations.

So we know that this approach works on DPI formulations containing actives for which dissolution is a rate-limiting step. So for instance, this publication from 2024 shows the study of three strengths of the same product, Advair Diskus. And we can see here that the aggregation state for the three of them was different. And therefore the dissolution profiles were different as well.

So if we look at the top of them, the areas graph. That's the high strength. That was the product with the highest fraction of standalone FP and the lowest fraction of aggregates, and therefore it was the one that dissolved the slowest. Meanwhile, the low strength that's at the bottom of the MDRS graph. That presented the lowest fraction of standalone FP, the highest fraction of agglomerates, and therefore it was the one that dissolved the fastest.

Now while it is established that this works well for slow dissolving molecules, when we look at formulations with fast dissolving actives like let's say an FF triple combination, I think we are still a bit in the dark when it comes to some aspects of microstructural analysis like for instance the drug release and its role in assessing the rate and extent to which the drug is deposited at the site of action.

And that is really the issue that I'm trying to address today. So we can see here on the slide this image, of course there are APIs missing here, but I think it's pretty representative of how the soluble APIs outnumber the insoluble APIs quite significantly, and if we want to study the release of these then we need an IVRT system.

So I think it's worth mentioning that there's a difference between dissolution and release. So in vitro release systems tend to load the drug on one side of the membrane that keeps it separated from the media. And then the media will wet or hydrate this membrane, and that's the first step in the release process.

The drug then gets in touch with very limited layer of media and we can think of the membrane as a mini sponge. So as the membrane takes up a bit of liquid, the drug that is on the other side of the membrane starts dissolving and then this is going to create a concentration difference between the receptor and now the donor compartment, which is where the drug is dissolving.

And so this difference in the concentration will make the drug diffuse through the membrane from the donor to the receptor and then hopefully within this release process, we will get to a steady state and that is where we can actually get the release rate of the drug.

So overall, dissolution and release are quite different, but we could argue that dissolution is equivalent to release when dissolution is the rate-limiting step.

So this is an example of an experiment that we did at Nanopharm. So here we compared the pMDI and the DPI version of Foster, and for this the active is BDP and for this experiment we used a paddle apparatus. When you try to analyze the dissolution of BDP it dissolves too fast to capture it with a dissolution apparatus. And so you need an IVRT system.

So if you look at the pMDI here, the red line, this is the DPI in blue and the release rate would be the slope of the equation. So we can see that the pMDI dissolves faster. And so, you know, clearly we're not comparing 2 DPIs here. It's a pMDI which is in an amorphous form compared to a DPI which is crystalline and also contains magnesium stearate so you know there are clear fundamental differences between these two formulations, but the key thing here is that the amount of dose collected for both of them was very similar.

And we can see that the release rates are different, so essentially, the crystalline drug permeates through the membrane at around 1/3 of the velocity we can see for the pMDIs. So this means that we can actually pick up microstructural differences and therefore that, you know an IVRT system could be really good for supporting microstructural equivalence.

So the previous data was generated with the system that we use at Nanopharm, but of course there are more systems that can and are currently being used. You know there's no pharmacopeia method at moment, so I think we are all just adjusting a variety of methodologies to use it for inhalation. So we have the Franz cell, that sort of replicates the diffusion-controlled air-liquid interface characteristic of the lungs.

Then we have the paddle apparatus which is more of a dissolution and diffusion-controlled test system. And here we have the membrane fully immersed in the media and then we have the flow-through cells that function more based on flow rate rather than diffusion. So here the drug release and transportation mechanisms would be a bit different.

I have included an example of each one here, but just to be clear this comparison is more general than that. Not based on those specific examples. So I'm looking at the data available in the public domain. Different studies do the assembly of the setup differently, collect the samples differently and so they get to different conclusions.

But yeah, I think we can all agree that the paddle apparatus is the most simple one in terms of handling, while the flow-through cell is the most efficient one in terms of the duration of the experiment. Then in terms of the amount of dissolution media, generally the Franz cell and the paddle apparatus tend to require higher volume of media. Meanwhile, the flow-through cell can work with lower volumes and so we could say that in this aspect, the flow-through cell is a closer representation of what the conditions in the airway tract would be.

And I guess this is related to one of the questions that are currently open, which is whether we need a method that is biorelevant and I will circle back to that in a minute.

And then we have the last two attributes, which I think are the most critical ones, which are reproducibility and discrimination power. I think in terms of reproducibility, the Franz cell and the paddle apparatus tend to give data that's a bit more consistent and then in terms of discrimination power, I placed them all in a medium ground because you know with data available, it's really hard to do a comparison on this really.

So there are many factors that could impact the discrimination power of a method like as I was saying, the sample dose collection or for instance the membrane selection. And so as I was saying, different studies were executed slightly differently. So the conclusions that they got to were different as well.

But you know, from what I can see, I think the three systems have potential and you know, yes, they get different results because release profiles can be sensitive to the methodology chosen. But you know, I think despite that, it's good to have different options because it will allow for more flexibility in research and so the point where I would like to get to is that I don't think we currently have a perfect IVRT system, but I do think it could be a really valuable tool for understanding microstructural differences as long as we have a discriminatory validated method.

And I think that's where the talent is. If at some point IVRT was added to the DPI generic program, I think we would need some level of standardization. And by this I don't mean that everyone should have to use the same method. But we should definitely have a defined set of parameters to evaluate during the development and the validation of this method to have a certain level of confidence.

And you know it. This technique may not add as much value for some of the drugs. For instance, the PSG for Tobramycin was updated last year. It doesn't include IVRT and it makes total sense because at the end of the day it's a spray dried drug and the only excipients are a bit of calcium chloride and the API. So you know, maybe you wouldn't get a lot of information out of these tests, but if we think of blends containing lactose or magnesium stearate, I think this technique can be really good for understanding differences in like for example, the effect of the excipients on the drug or the particle size.

So to conclude, as I was saying, IVRT was successful in transdermal particularly in the topical area. I think in the inhalation field the relevance and the value of this technique is really molecule specific. And you know, I think ideally, having a method that allowed to do an in vitro-in vivo correlation assessment would be great. I don't think that's the current situation, but I do think the IVRT method can be used for identifying microstructural differences between formulations and you know identifying differences in excipients manufacturing process particle size.

So just to finalize, I think further research is needed to define the role of IVRT in supporting Q3 structural equivalence, but I do think that having a discriminatory and validated method, this technique could have potential. Thank you.

Moderator
Alright. Thank you, Nuria. So for our next talk, it'll be given by Dr. Naresh Mittapelly. He's a research scientist at Certara UK Limited, and the title of the talk will be "Application of Mechanistic PBPK Modeling to Understand Drug Release from PLGA-based Solid Implants."

Naresh Mittapelly (Certara)

Thank you, Brian for the introduction. Hi everyone. Good afternoon.

So the topic of my presentation is application of PBPK modeling for understanding the drug release from PLGA-based solid implants. So this is the outline of the presentation. In this presentation, I'll try to cover what are the scientific and regulatory considerations to be given for the development of generic long-acting injectable drug products. How modeling and simulation can help in this process?

So this is the outline of the presentation I have. Introduction. I'll discuss challenges to establishing equivalence. I have two case examples with me. The first one is modeling of in vitro release from PLGA-based solid implants, second case example is about in vitro-to-in vivo extrapolation of drug release data for PBPK model development of goserelin solid implants. So lastly, I'll talk about impact of critical quality attributes on bioequivalence outcomes using virtual bioequivalence module of SimSB Simulator.

So let's begin the presentation with introduction part. So long-acting injectable drug products, commonly known as LAIs. These products include polymeric implants, microspheres, suspensions. They are considered to be complex drug products because of complex formulation in nature. Because of complex formulation in nature, the development of generic long-acting injectable products can be challenging to the pharmaceutical companies and at the same time can be rewarding. In order to develop the generic long-acting injectable drug product, the sponsor must establish different levels of equivalence, which we can broadly classify into qualitative sameness, quantitative sameness, and most importantly, physical, chemical and structural similarity.

So together these criteria will ensure safety, efficacy and performance of a drug product with respect to reference product. I don't want to go into the details of Q1 Q2 Q3. I think by now everyone is aware of this.

So challenges to establishing bioequivalence: making generic long-acting injectable versions presents unique scientific and regulatory challenges. These formulations require overcoming hurdles during the development, manufacturing, during testing and bioequivalence analysis. So I will cover three key different challenges.

The first challenge is complex formulation and manufacturing understanding. A formulation is first step in developing a formulation. So for example, for PLGA-based systems it is essential to achieve same composition, molecular weight and drug release as that of a reference product. For nanoparticles liposomal preparations, it is necessary to control the particle size distribution and control the encapsulation methods during the manufacturing because these are going to impact the drug release. For particle suspensions, it is the particle size distribution and particle stability. These are two important factors to consider while developing the formulations.

Drug release and PK profile matching. It is difficult to establish direct in vitro to in vivo correlations for long-acting injectable drug products because of complex release mechanisms and long duration of study. From PK standpoint of view, the sponsor needs to match the burst release phases and slow release phases with respect to reference product in order to establish therapeutic equivalence.

From bioequivalence standpoint of view, the sponsor must pay attention towards practical considerations. For example choosing between parallel study versus crossover study, recruitment of individuals into the study, addressing the variability that is coming from patient

response. So these are some practical challenges the sponsor must consider during the development of long-acting injectable drug products.

So these challenges make the development of generic LAIs a complex and rigorous data-driven process.

So before going into the case study, I would like to talk about the model that we have in SimSB simulator that is developed to explain the drug release from PLGA-based solid implants. As you can see here on the right hand side, we have a solid implant in contact with the release media. This is the model structure and we have two sub-compartments within the solid implant that is unwetted compartment and wetted compartment. Based on the degree of wetting of the implant.

So we have considered different processes that are known to happen when the solid implant is wetted. So we considered non-catalytic heterogeneous degradation of PLGA, which is nothing but PLGA degradation products itself increase the hydrolysis of PLGA. We also consider dissolution of polymers, dissolution of drug, liberation of API from unwetted compartment to the wetted compartment. So these are the known processes that are reported in the literature.

In terms of model parameterization, we would require different model parameters that are coming from different sources. They can be broadly classified into drug physical-chemical properties, polymer and formulation information. Other parameters: drug physical-chemical properties are nothing but molecular weight, solubility, pKa information, polymer and formulation characteristics like implant dimension, polymer molecular weight, polymer lactate to glycolate ratio etcetera. Other parameters like we need pH of the media, volume of the media. So these are the parameters that are used during dissolution or release experiments for PLGA-based solid implants.

The key difference between in vitro model and in vivo model is in case of in vivo model, we have a solid implant in contact with the interstitial fluid. As you can see here this interstitial fluid is in contact with the local site compartment which is nothing but in case of goserelin it is adipose site compartment and this interstitial fluid compartment is again in contact with the systemic compartment. From this interstitial fluid compartment transfer would happen to adipose site compartment and systemic compartment. So this is the key difference between in vitro and in vivo model.

So the first case study is about goserelin solid implants. The goserelin solid implants in literature from Sandor's publication we have different release profiles. They have manufactured different implants by varying the lactate to glycolate ratio ranging from 80:20 to 100:0. So we have different release profiles from these different formulations.

It's goserelin. It's a gonadotropin-releasing hormone agonist used for the treatment of endometriosis and early puberty. So we have physicochemical properties information. We have formulation information. Formulation information from the same publication. Here you can see the parameter values. You know implant parameters. We have formulation characteristics. If you notice here in red color, we have some of the information missing from this particular publication and from literature in general.

So for these lack of data, we have assumed, for example, fractional volumetric porosity. We have assumed certain percentage here to run the simulations. From in vitro release condition side, they have reported release in pH 7.4 ethanolic phosphate buffer. However, they have not reported volume of media, so we have assumed it to be 10 mL.

So here you can see here we used first formulation that is 80:20 in order to develop the model in order to parameterize the model. This was achieved by varying by changing ionization proportionality constant and deionization proportionality constant. These parameters are going to affect the degradation of PLGA, so for this particular formulation, we have optimized these two parameter values in order to fit the observed data.

So this is the drug release profile. It is in this figure you can not only see the drug release but also other model outputs like pH of the intra-implant compartment. How the molecular weight is changing as a function of time. Also, how the release media pH is changing as a function of time? This kind of outputs and comparison is important when you wanted to understand what exactly is happening and how you want to understand it by comparing it with the different outputs. For example, in case of in vitro drug release, a certain change in drug release happens when the pH of the intra-implant phase is dropping from 8 to close to 0 value in the micro environment.

Also, how the molecular weight is changing suddenly - average molecular weight is changing from 20,000 to around 5000 and how it is correlating with drug release? So this kind of information is important when you want to understand the release mechanisms.

So this is the model performance for other formulations. In order to run these simulations, what we have done is we only change the lactate to glycolide ratio to run these simulations and how the model is performing you can see in terms of observed data versus simulated profiles.

In general, when the lactide content in the formulation is increasing, there is a delay in drug release that is observed for these formulations and also we have seen there is a discrepancy between observed data and the simulated profiles and this can be attributed to you know changing Q3 attributes because what we have assumed is for all these formulations, we assumed a similar Q3 parameters like porosity you know. So if we incorporate that information, there is a possibility of you know increasing increase in closeness of observed data with simulated profile.

So the second case study is about goserelin solid implants. For the goserelin solid implants, we have release data from Shlikar publications. So in this publication they have reported the implants dimensions, implant composition, and they have provided the release profile. So in this publication we only have one formulation data. So which we have used for the model parameterization.

So this is the overall workflow for in vitro to in vivo extrapolation. So first we carried out in vitro release modeling. Separately, we carried out intravenous PK model development for parameterizing the model for distribution and elimination phases. Then later these two models were combined to develop PBPK model for 3.3 mg solid implants. And after development of this model, we validated it with 6.6 mg implant data that we have in literature.

So here you can see the results. This is in vitro release fitting and after fitting the in vitro release. When we developed and simulated here you can see that 3.3 mg implant data and the third figure is about 6.6 mg implant validation, validation how the model is performing.

So in order to develop this in vitro to in vivo case example, we assumed the in vitro release studies reported is considered to be biopredictive in nature. So that was the main assumption we had for developing this case example.

So lastly, what we have done is after developing the PBPK model, we transferred this model into the virtual bioequivalence module of SimSB simulator and studied the impact of critical quality attributes. Two critical quality attributes, namely lactate to glycolate ratio and PLGA molecular weight. So when we changed these two parameters, you can see how the Cmax, AUC and AUC infinity are changing when we are varying these parameters in certain range. This kind of information is important when someone is interested in doing in silico experiments and how the critical quality attributes are going to influence your formulation performance at the level of population.

So in summary, in this presentation I have discussed different challenges for the development of generic long-acting injectable products. So we have identified some gaps in this area. For example, the first one is reverse engineering of solid implant for the branded products, testing of implants using biorelevant and biopredictive methods, characterization of implants for mechanistic understanding of drug release. These characterization studies can have PLGA molecular weight change as a function of time, water uptake profile, porosity, pore size change as a function of time. So these kind of mechanistic studies can add value to the models and help in validating those models.

In addition to the RLD, it is also equally important to study the alternate formulations and how those formulations also behaving in the similar release conditions and these experiments can increase the confidence about the models.

So the take home message from this presentation is the in silico modeling can go hand in hand with empirical release testing for a better understanding of drug release and optimization of formulations during development.

So I would like to acknowledge my team at Certara Predictive Technologies and supervisors. I would also like to thank my collaborators and organizers at US FDA. Thank you very much for your attention.

Moderator
Alright. For our last talk, we have Claire Butler. She is a principal product development scientist in respiratory R&D at Teva Pharmaceuticals. Her talk will be "The Utility of In Silico Modeling and Substitution Risks for Generic Orally Inhaled Drugs."

Claire Butler (Teva)
So thank you, Brian, for the introduction. Firstly, I'd like to extend my thanks to the organizers at the FDA for the opportunity to speak here today. It's my first time at the FDA and I'm really happy to be here in person. Meet everybody.

So. This is my disclaimer slide.

So briefly, I'll just I'll firstly take you through the contents of my presentation. I'll talk a little bit about current bioequivalence risk mitigation for inhaled products. I'll touch on using a case study example how we've developed and validated PBPK model and how these models can be used in the overall BE approach.

Similarly, I'll use a case study example to touch on how we've developed a lung deposition modeling model, specifically semi-empirical model. And the challenges we've faced with validating such a model and its overall relevance again with respect to the BE approach.

I'll talk a bit about the scope of the CE waiver approach with respect to Q1/Q2 products or Q1/Q2 same products and how this could potentially be expanded to include risk-assessed non-Q1/Q2 compliant generic products. I'll touch briefly on considerations surrounding generic device design and close with a brief summary.

So first of all, you know there are considerable risks associated with demonstrating bioequivalence for oral inhaled drug products. You know, inhalers are called complex combination products for a reason and as per the you know the option one or CE waiver approaches in many of the new PSGs there are mitigations available to us and you know with respect to these risks.

So if you look at the device in the first instance, we have to ensure that we develop or essentially copy the device to ensure that the patient obtains the same efficacy and safety associated with this device. Or with the device and we do this through quality engineering and user steps comparability, which I'll touch on a little bit more in a later slide. And so any changes to bolus volume or delivered dose associated with the generic inhaler can mean that the patient either obtains a suboptimal dose or indeed an overdose, and we mitigate against this risk as per the current PSGs be they option one or CE waiver approach or otherwise by conducting IVBE on dose content uniformity and other pMDI specific tests, such as plume geometry on spray pattern and of course one of the single most important risks to ensuring that an inhaler does what it's supposed to do is how the patient uses this. Uses the inhaler and we can somewhat control for this within clinical studies. But of course we can't replicate the same control measure you know in the everyday lives of a patient.

And so this is where appropriate training comes into play, which is married into, I suppose, the clinical design within your PK study or clinical. How the drug regionally deposits within the lung, of course affects how the drug performs in terms of efficacy and safety and we mitigate against this risk by performing formal IVBE on the aerodynamic particle size distribution of the drug and of course every patient is not the same. So within the patient population, there are variability or differences in terms of their lung geometry and or pharyngeal geometry and that's why we now see the introduction of realistic APSD methods that use patient breathing profiles and realistic mouth-throat models.

So changes again to the physicochemistry of the drug, or the microstructure can change how the drug deposits within the lung and how it's absorbed and this is why we now see the introduction of comparative characterization of the emitted dose in terms of structural analysis. Changes to dissolution, of course. You know, especially for poorly soluble molecules can mean that either the drug is retained within the lung for too long, meaning that the drug doesn't have its therapeutic effect, or indeed it gets out of the lung too quickly, posing a safety concern and this is why we now do or, you know, see the introduction of formal IVBE, of dissolution, or physiologically relevant dissolution studies.

And of course, any change to these risk factors you would imagine or you should see in terms of changes in systemic absorption and this is why we of course conduct formal BE pharmacokinetics and if you can, if you want to use the optional PBPK or modelling approach within the PSGs these can help with assuring bioequivalence prior to actually conducting the clinical PK studies.

And so this slide really emphasizes the progress that's been made over the last, you know, six years or so in terms of the introduction of alternate BE approaches within PSGs for orally

inhaled drug products. And what's fantastic to see since 2024 is that some of these PSGs exclusively removed the option for the CE study, so they're just not there.

But I think where industry would benefit is understanding the scientific rationale between either removing the option, the need for these CE studies or leaving them in there for an option as an option and one specific example of this is, you know, quite recently there were PSGs issued for ICS/LABA pMDIs, which have drugs that have similar physicochemical properties, similar or same formulation technology. One of the PSGs just did not have the option for the CE study and the other, you know, the option was still there. So again, just to reiterate, understanding the scientific rationale for those decisions would be quite helpful.

And so in the cases where it's possible to follow an optional modelling approach within the CE waiver studies or CE waiver approach, the ask is to develop and validate a PBPK model. And so we looked at this using GastroPlus and we developed a mechanistic PBPK model for fluticasone furoate dry powder inhaler.

And so we developed this mechanistic model using a reference product reference product, a target test product designed to perform the same as the reference product and a test product designed to perform differentially to that of the reference product. And we parameterized this model or this mechanistic PBPK model using data from realistic APSD methods which use breathing profiles representing representative of the target patient population and realistic mouth-throat models such as the OPC model that you can see in the image to the right.

We also parameterized this model with dissolution data using physiologically relevant methodology. In this instance paddle USP, paddle over disc apparatus. We also then developed for this PBPK model and validated a compartmental or systemic disposition model. We use data from a literature-based study that administered FF intravenously.

We also parameterized the model with drug-independent data pertaining to pulmonary regions, regional surface areas, epithelial lining fluid tissue volumes, etc. And drug-dependent parameters such as solubility, diffusion, density, molecular weight, etcetera.

And so using the model that we developed in the previous slide, we generated area under the curve or predicted area under the curve and Cmax values pertaining to the three batches. And in order to validate the GastroPlus PBPK model, we then dosed these three batches in a clinical PK study when we compared the output data in terms of Cmax and area under the curve from the clinical study to that of GastroPlus, the data agreed really well.

And so the take home really from this and from this slide is that PBPK models can be successfully developed and validated and can be used as an assurance of clinical clinical PK BE, which essentially expedites the product development process and access to generic products.

And so using the optional or the optional computational modeling modelling CE waiver approach, one of the asks also is to develop and validate a lung deposition model. And so we looked at how we might be able to do this by using an inhaled triplet formulation of tiotropium bromide. And again using Medicus GastroPlus, we generated predicted regional lung deposition data. And then endeavored to validate this using literature-based scintigraphy study published by Brand et al. where they radio-labeled tiotropium bromide and dosed it in a scintigraphy study.

When we compared central to peripheral data from that of GastroPlus for healthy and diseased patients to that of the scintigraphy study, we saw some really close alignment, which sounds great, right? Well, yes and no, because we couldn't say with absolute certainty that we were comparing apples and apples to apples.

So with respect to GastroPlus, the output is defined by that of the Schroder mapping, so it includes a central peripheral and an intermediary region, whereas the study by Brand et al. only defines only defines central and peripheral regions and so we had to make an assumption that the intermediary regions within the literature study distributed to central and peripheral regions in proportion to the contribution to CMP.

So the only way to really overcome this you know, this assumption would be to conduct our own clinical study where we radio-label our product and do it in a scintigraphy study. And you know unfortunately this adds you know it's kind of similar to the paradigm of the clinical endpoint study. It adds to the overall duration of the drug development process. Ultimately, you know, increasing the timeline to getting these products out to the generic market.

And you, you know, the research question is, you know, could we more so rely on metrics of pharmacokinetics to inform on regional deposition sameness. And you know what, what types of endeavors would we need to look at to be able to, you know, to really rely on PK BE? And I suppose the ultimate question is, if you have a test and reference product that performs the same in terms of systemic exposure, what is the likelihood that that the test product has a differential lung deposition patterning? How do we address that? How do we how do we look at that?

And so if the option for the product that you're developing can use a CE waiver approach or an option one approach and it's Q1/Q2 the same. You can follow the paradigm on the left hand side of the screen whereby you don't have to rely on a clinical endpoint study which we know is very insensitive. And you don't have to rely on validating optional computational models. And what this results in is timely supply of quality generic inhalation products, which is what we want to achieve ultimately. But as Ross alluded to earlier, you know, there are instances within the 505(j) scope where we cannot be Q1/Q2 the same.

And I suppose the question is in those instances, if for a product that's not Q1/Q2 the same, that's been risk assessed to perform bioequivalently in terms of systemic exposure, can we then revert to the paradigm on the left hand side of the screen for those products and follow an approach whereby we don't have to rely on clinical endpoint study and we don't have to rely on, potential additional clinical imaging studies.

So again, I've just reiterated here in this slide what I've just said. So where the risk is assessed and the Q1/Q2 deviation for the generic or 505(j) product does not affect overall systemic exposure, can we follow a clinical endpoint waiver approach without having to validate optional computational models?

And so whilst device design isn't within the specific scope of this particular sub-session, I think it's really important to highlight it because you know the device is you know such an important interface between whether you know the governing whether the patient receives the correct dose or not, you know and as a specific example when Teva genericized the Advair Diskus product and we looked at the function of the thumb lever in that device. The function of the thumb lever is to you know, peel back the blister foil within the internal constituents of the device and make the drug available for inhalation.

We would have been able to remove that step and essentially offer the patient with an open-breathe-and-close type type device, essentially making it easier for the patient to use the device and potentially addressing adherence to the medication, ultimately reducing patients or healthcare burden with respect to respiratory disease and you know as an add on to this, there are proprietary products that have been on the market for 10-15 even 20 years before they're genericized.

And the question is, you know, some of these devices actually have inherent design flaws. Excuse me, have inherited inherent design flaws and you know, given the current user steps comparability you know we can't improve upon the device design. And so ultimately the question is how can we improve upon device design within the overall BE approach while still maintaining BE?

And so in summary, the risks associated with generic substitutability can be appropriately mitigated for Q1/Q2 compliant products using CE waiver approach all of the risks can be mitigated within this paradigm. PBPK modelling can be used and successfully validated to serve as an assurance of BE prior to commencing clinical PK BE studies.

Validation of in silico lung deposition modelling is quite challenging, given the lack of comparable literature-based scintigraphy or imaging data that is available to us and the only mitigation to this for us is to conduct our own clinical studies which can often take the same time frame associated with that of a clinical endpoint study. So again, you know, it doesn't help with expediting the product development process and getting generics out to patients quicker.

And then, you know, so could Q1/Q2 non-complying generics be considered as eligible for CE waivers, so long as we risk mitigate and ensure that we've got similar systemic exposure BE. And then in terms of user steps comparability for device design, how can we improve upon device design within the current overall BE approach?

And that concludes my presentation. So thank you very much for your attention.

Moderator
Alright. Thanks Claire for that wonderful talk and I'd like to thank all the panelists and or all the speakers rather that presented today. I think it helped drive home the point of the complexity with understanding where in vitro studies are going to play a role, understand which studies are the most appropriate and then how they can be informed by in silico modeling, how there can be a link between that to ultimately understand clinical performance better so.

With that, I want to reiterate that if there's anyone that wants to give any public comments that the microphones in the middle are available, so please feel free to do that. But this would we can start the panel discussion so.

Panel Discussion
One of the first questions I'll ask is certainly this will be directed to Andrew here. When developing a mechanistic model for generic topical dermatological and orally inhaled products, particularly those with Q1/Q2 differences from their reference products. What? What are the key knowledge gaps that are still needing to be addressed here?

Andrew Babiskin (FDA)

Yeah. Either one. Sorry, I just had a clarification there. So I'll touch upon topical dermatological products and I'll call upon Ross to talk about the inhalation. Now it's been about a little bit over an hour since Ross gave his presentation, so we need a topical dermatological example of how we can apply in silico modeling mechanistic models to approach bioequivalence for non-Q1/Q2 topical products.

But let me kind of like recast that like we proposed there some different parameterization such as like evaporation thermodynamicity. There's even things about how the product is physically manipulated when you're when you're applying it. All these factors are important, regardless if it's a not Q1/Q2 or Q1/Q2 product.

Ultimately, when we're developing these platform for these models, we have to look across many different products where these factors could be different and it could explain why certain products don't perfectly work with those bottom up approach purely bottom up approaches because there's some sort of physical process or chemical processes not described.

So it's good that we're incorporating this through the through the research now get the benefit when it's cumulative 2 that we don't expect these processes to be be all that different when you have the same exact excipients, so it's kind of you can de-risk the model. Are there any uncertainty in those parameters you can still use some you're better able to justify optimization of those parameters and look at the sensitivity of those.

But when we're getting into the not Q1/Q2 space, that's where it gets a little bit more important because now we have to to understand all those different excipients or excipient levels are directly related to these processes. And so we're all doing this through like always the main driver for all these products is, was the impact on the ultimate permeation, the product we can utilize IVPT studies towards validation of these ultimately.

For Q1/Q2 products, we want to see that OK, everything is permeating the same, but it's the same exact thing for the non-Q1/Q2. Are these products still continuing to permeate the same? At the same amount.

Ross Walenga (FDA)
Yes, for the inhalation. I think like you mentioned Claire, with the deposition modeling, we do see some gap in terms of availability of validation data, so. I didn't mention one grant that we've awarded, where we're gonna be hoping to conduct in vivo study and the expected output of this would be imaging data that's not necessarily specific to one active ingredient, and that it would provide the corresponding CT scans and all the information that someone could use to validate a model, and we're hoping to do this with two different conditions so that you can show that the model has the ability to discriminate between different formulations.

So that's one way we've been trying to fill that gap that we're still working toward that and that would be for MDI. So we would, there would still be a gap for DPIs. So one area we've been working toward, other gaps I would say would be for PBPK just in terms of parameter parameterization, which is always a problem with PBPK. But I I've done some recent modeling and one active ingredient I looked at was kind of woefully lacking in terms of parameters. So I think that there could be a lot of work to be done just for basic parameters like blood to plasma ratio even.

Moderator:
Thanks Ross. So before we get to Charlie, does anyone from the panel want to talk for this?

All right, Charlie, do you want to provide comment?

Charlie Montclair (Bioequivalence Services) I would urge the Agency in the development of bioequivalence standards for topical dermatological products to consider that the most fundamental aspect of drug delivery, in other words the dose, is generally uncontrolled for the vast majority of such products. The dosing device is typically the fingertip and it's metered by how big a dollop of the goo you put on your fingertip before you apply it to the affected site. So please, let's not come up with overly restrictive or narrow bioequivalence criteria based on fancy, in silico, PBPK modeling when the dose is basically not controlled. Similar comments for ophthalmic ointments. I can't even get the stuff in my eye sometimes, much less meter the dose accurately. Thank you.

Moderator
Great. Thanks.

Unidentified Speaker
Yeah. Thank you, Charlie, for the question. I believe the dosing and topical administration mainly depend on the device that we are using during IVPT testing and usually we are using some objective dosing techniques to standardize those that are applied during in vitro permeation testing. However, for clinical study also, I think the IT should be controlled clinical application. So even the dosing personnel is using objective study to dose the skin so that we are ensuring it is consistent amount of dose that's applied to the skin.

Dr. Markham Luke (FDA)
Yeah, I think Charlie's correct. The clinical dose does vary, but we do want the products to be as consistent as possible with the reference product. So both from for look and feel, and also for the delivery rate of the API when applied to the skin. So if a patient is used to applying a certain size dollop to their skin when they get the generic, we want them to have that same effect with the same size dollop.

Some labels will actually specify a golf ball size or pea size amount, so we we had patient-friendly descriptors when we were in new drugs to how much to put on on a patient. But you it is somewhat user dependent, but at the same time from the generic perspective, we believe that it's important to have a similar product as possible.

And then, Claire, I liked your comment about the device aspect. So we are working on seeing what we can do to have generics evolve their device as well, like you can come on the marketplace with something that is similar to the reference product. But as the reference products change and as the standard for devices changed as the years go on, allowing for changes in supplements etc. These will come up because we're just now allowing the first relatively first few drug-device combination products to come out in the marketplace in the context of 505(j)s as the years go by, those products will have to change and accommodate based on technology patient preferences, things like that.

So we'll we'll have to think about that as a as a future development, and it's a research project and so there, there are studies that can be done. There are delivery studies and etcetera and this is where we put our engineers to work and industry also puts its engineers to work. Thank you.

Moderator

Thank you, Dr. Markham. So on the same line of talking about compositional differences. So let me ask the Industry Panel first about the permissible formulation differences. Usually Q1 and Q2 is defined by 5% difference in in the composition. So what do you think from your perspective? What would be the research gaps or research areas to study the permissible formulation differences? For example, like if there is any ongoing effort do you think we should focus on revisiting Q1/Q2 same standards or recommendations for inhalation product and for topical product. So let's start with Andrew.

Andrew Cooper (Viatris)
I think this is an important issue. Because from an industry perspective where we have kind of arbitrary limitations or formulation differences that, for example push you towards doing a CE study, you know that still represents a barrier to to product development to generic product development. And to be honest, I actually suspect that the kind of battery of tests we've got in option one may turn out to be more sensitive to factors affecting local equivalence than the clinical endpoint study. But I think that one of the features of what you might call the new weight of evidence that we really need to understand is you know what is that sensitivity to formulation differences?

So if we can start to look at research that joins up the in vitro, the in vivo PK outcomes for Q1/Q2 differences. That would be that would be really useful because to be honest, I think there are so many reasons why you might need to have a formulation difference. That's why this is a really, really important topic, and I think as with a lot of things, I think if we can rather than have arbitrary limits look at a risk assessment based approach where you, you kind of look at what the functional attributes of the formulation you're trying to control through the formulation difference that you're making, or maybe are forced to make.

What are the potential unintended consequences? What are the risks to local delivery and then construct a risk assessment that then says, well, what development experiments do I need to do to to ensure that those risks are mitigated within my formulation design space? So I think that kind of approach which is the kind of approach we use for a lot of other things is is a much better approach than having than having arbitrary limits and ending up, you know, maybe limiting your ability to actually develop a generic product.

Moderator
From FDA side, what do you think about the compositional difference like the limits for Q1 and Q2 similarity?

? (FDA)
Yeah. So I think in in my perspective, I think the concept of permissible formulation difference, it's kind of a critical aspect in terms of ensuring the therapeutic performance equivalence. And you know for the generic versus the brand and also you know allowing the formulation flexibilities around that. But I guess you know it's important that you know at least from the defining what could be allowed and how could be applied for generic development.

It really depends upon you know what those differences are. And you know if the applicant is able to demonstrate that you know, identify and characterize those differences, that it's not going to affect the safety, you know and efficacy of the product and enabled for the demonstrate through the individual you know in vitro BE studies, you know which is talking about for inhalation products, especially demonstrating that.

But you know, for the excipient range studies and you know, understanding the effect of the level of excipients and understanding the effect on for example on metered dose, you know understanding the effect on how that would affect the CQAs in terms of the delivered dose uniformity and aerodynamic particle size distribution, including the fine particle mass, which is kind of a critical mass which is deposited in the lung cavity.

So thinking that could be built on the, you know in in some kind of studies and if we can build on an IVIVC or IVIVR, I think that could allow certain permissible differences. At least from the inhalation perspective, and I think we spoke about, I think the presenters gave a nice, you know, talks about in terms of mechanistic modelling. You know I think that's another approach, you know PBPK modelings and in silico models. I think those are some of the ways to, you know, correlate in terms of, you know, understanding whether those method can be a biopredictive in understanding the performance, clinical performance of the products and I think we have done a significant you know efforts in terms of allowing in understanding this Q1/Q2 differences and as you can see from the PSGs for inhalation products for MDIs and DPIs any agency has made advancement in in after you know, through the academic research and allowing those optional based you know so I think. There's always. Thank you.

Moderator
Claire, I think you mentioned in your presentation about the mitigation for Q1/Q2 different formulation. So, so for some of the excipient trials, it difficult to show similarity, especially when it is heterogeneous excipients or it's a mixture of excipients to in one material. So what do you think? Like how we can mitigate this difference so that it does not affect the bioequivalence and we can revisit the standard in this case.

Claire Butler (Teva)
So I think just you know to you know, not to overly trivialize or you know simplify it. I mean in instances where, say an excipient needs to be different to, you know, deviate from perhaps infringing on a patent or some other instance. I mean, if you can show using the suite of in vitro bioequivalence tests in terms of you know structure and morphology dissolution, APSD, realistic APSD. All of these methods. That the product performs the same and ultimately your systemic BE is the same.

Then you know there's the mitigated there's the mitigation paradigm, and if, you're substantially different than you're outside of the 505(j) territory, you shouldn't even be. You shouldn't even be looking at that regulatory pathway. So you know, hope that answers the question. I hope I interpret it correctly.

Moderator
Yeah, to some extent for this exception. Do you think we can rely on maybe 10%, for example, or what kind of research that's needed to support change?

Claire Butler (Teva)
Standard room, you know, in terms of extending limits, again, I think it's very product molecule you know context dependent. You know and whereby if limits could be extended, I mean really it's the question is, are we altering safety and efficacy. And if not, and perhaps those limits should be widened?

Moderator
Thank you. Wenlei, continue, but from your side.

Wenlei Jiang (FDA)
Yeah. Thank you for this question. I kind of agree with our industry speaker for some of the inhalation products, the compositional difference, we really need to look into excipients to see how critical they are to impact the individual performance first and also like systemic PK and with that information probably can mitigate the risk and we probably can expand some of the difference in the excipients in the formulation.

Actually. I do have some clarifying question. I want to ask our speakers if time allows. Actually, one of the questions I have is regarding the in vitro release testing for the OIDPs I think. Nuria presented at the data on the flow through cells and also the paddle method and the Franz cell. And I think you have a very nice summary about some of the strengths and weakness of these methods. And I think you mentioned that the flow cell flow cell method has low reproducibility. I just wonder if that data is kind of widely observed in literature or just from your company's data. Thank you.

Nuria Jurado (Nanopharm)
No, thank you for your question. So this is all from literature. I haven't used it personally. Again, this was just a general observation I think. Some data from inhalation sciences using this, Ovid was released very recently. A couple of days ago. And I think that's an example of a flow through cell. And actually the data I think it was really good. So, you know, I think that's an example of consistent data that you can actually get with a flow through cell that was more of a general comparison of the state I had found in the public domain, but as I said, it's a bit hard to make a comparison because different studies will give you slightly different results.

Wenlei Jiang (FDA)
Yeah. I just wonder if there's any like explanation about the low reproducibility observing the flow cell system, yeah.

Nuria Jurado (Nanopharm)
So. I think the reproducibility can be impacted by how the sample is collected, for example, or you know the membrane selection. So I think this specific studies that I was looking at may have been influenced by that. But if the selection had been different, perhaps the outcome would have been different as well. I don't know if that answers your question.

Wenlei Jiang (FDA)
Thank you.

Moderator
All right, so this question is for Naresh. So what are the key challenges in current and future research that limit its use in informing in silico models for accelerating developments for complex long acting injectable products?

Naresh Mittapelly (Teva)
Thank you very much for the question. So currently we are working with FDA on addressing some of the gaps that we have in in vitro release for in silico-based approaches. So basically the gaps that we see is biopredictive testing of different solid implants or PLGA based systems. So there is one gap that we have identified.

Second gap is about validation of release mechanisms using suitable experiments. So most of the times when people are running some in vitro experiments, they are only interested on drug release. But there is a need to investigate on other aspects like PLGA molecular weight change.

How the porosity of system is changing? So these are some of the gaps that we have identified with respect to you know PLGA based systems and apart from that in terms of validating the models, this is important because when you want to use in silico models for making some decisions regarding the equivalence of the product and subsequently using it for bioequivalence testing.

It is necessary to validate those models with the experimental data and there has been a. There has been a discussion on this from both regulatory side as well as internally etc. Are predictive technologies. So I see these are the some of the gaps like alternate formulations like by varying the composition of the system. As the sponsor or public researchers may make those formulations and study how the changes in these in those formulations Q1Q2 and Q3 level changes in the formulations or making differences in terms of drug release.

So these aspects need systematic study and it is noteworthy to mention that the PLGA, degradation and implants fabrication is sensitive to the API, so you cannot just consider one API study is applicable for all the APIs that are available in the market. So these are some of the considerations and gaps need to be.

Moderator
And thanks for the lists. So I guess I wondered. Do you have any consideration on which one might be like the greatest priority? Which one would you want us to focus on first?

Naresh Mittapelly (Teva)
So I think it is important to look at the biopredictive dissolution release experiments. Because you know you can get different profiles for different solid implants when you place them in different release media. So what is relevant is for successful utilization of in silico modeling and subsequent transfer to the in vivo models, it is necessary to have biopredictive method so.

Moderator
Alright, so Hailing did you want to comment on any of this?

Hailing Zhang (FDA)
It is working yeah. Yeah, I agree with, with the race comments. You know, we in the submissions of some of the model we see lack of understanding the mechanism behind release and also the drug depot formation seems limited. The utility of this model. I think to have this type of understanding definitely will help. Hope strengthens the model in terms of the development of validation and also we also see lack of understanding of the release kinetics.

In some of the models we saw in the submission, we see. There is an arbitrary kind of divide between like, burst release versus prolonged release with, with, not without much kind of experimental data support. So sometimes it's very hard to really to make a regulatory decision based on model if we don't really understand how that model really works. So. So I think agree with the speaker's comments in terms of the gaps in the priorities.

Moderator
Thanks Hailing.

Maxime Le Merdy (Simulation Plus)
Can I just add one thing here, sorry. There's still one tree to consider, especially for LAIs. However, we made that in vitro study complex and informative and so on. We don't see if we

understand what's happening at the depot side in terms of inflammation. Look at blood, local blood flow, etcetera.

So until we get a good understanding and a good model for the physiology, you can make an in vitro study as fancy as it is as complex as it is. You still not gonna be able to have a correct I. VIVO IVIVC IVIVR, whatever the name is because of that. So lots of effort has to be done on understanding what type of depot you are mentioning, the burst versus the slow release. It could be related to inflammation.

We've noticed the blood flow change been change. If you are like fasted or fed like surprisingly, but the muscle blood flow that changes because of that. So there's many factors at physiologically related and not formulation related and we can focus. I mean, I understand the concept for generics. We're focusing on the formulation, but those tiny change in the physiology can have a huge impact.

It has a huge impact between patients as well in their subject between location administration, so also and maybe to go back to the point that Charlie made is are we tracking the impossible because we're going to make a product that is going to be very, very similar, very compatible but in real life and I think that was Charlie's question is not really in the context of like the histories, but in real life, does it matter? Because in the end you get 200% variability. So to go back to your point, like 5% variability in the excipients, does it matter?

Moderator
Yeah. Thank you, Maxime. So I believe that the dissolution testing and drug release is one of the most important or I would say not the most among the most important factors to be considered even to inform modeling or to understand the performance. However, we usually like go for the standardized tests and preferably it should be biorelevant method and thinking that the bioprediction would be guaranteed.

But in actual situation, not all biorelevant method has to be necessarily biopredictive and from quality perspective it may be even complex to be applied for quality purpose. So let's move a little bit to what our expectation is when we are talking about biorelevant methods, either for dissolution or realistic aerodynamic particle size distribution. What type of research is needed to improve both bioprediction as well as biorelevance of the method? So let's talk about dissolution first. Xiaoming, do you want to comment on this?

Xiaoming Xu (FDA)
Yeah, I may be stepping back a little bit. I think the previous conversation is also related to this one, which is what's important as we study and set goals for research versus what's practical in patient settings. So I do want to recognize we discuss a lot about tool development or method development, dissolution, IVRT modeling. These are tools used to understand phenomena.

And we are talking about the product that we, the companies as developers, develop. You need to show how much you understand all the factors going into making the product successful. And of course, the tools are what we use to measure whether or not we can verify those successes realized, but we cannot really break the link between the understanding of the product versus what we are trying to measure.

To the extent even how to decide on which measurement and the value, whether it's dissolution or this model correlation, how do we decide if they really give us confidence? It all needs to link back to what we understand is critical. If the product is designed with an excipient that imparts a

critical function for delivery or release mechanism, then it becomes very critical to ensure the design of the product. The excipient is rendering the same effect.

So then for dissolution, as we understand what the mechanism or what really functions, then we can design in vitro dissolution, whether it's for inhalation product, topical product or dermal product. Then we can design in vitro measurement to tell us if we do expect the differences in the formulation, which is critical differences of the material or process. Can we see the differences?

So I think that connection is very critical, but sometimes as we overly focus on the tools, the methodologies, then we may disconnect even with what is the kind of the overarching design aspect which of course the companies know more about from the design. Which, if you can demonstrate in your submission even your full understanding about what's critical, then that also will provide some flexibility in terms of the regulatory because the whole paradigm is based on de-risking. You know, do we understand enough or do you understand enough? If we can see that you understand enough then certainly certain risks can be de-risked. I don't know if I'm answering your question that you're asking, but it's been a very interesting discussion.

Moderator
Yeah, I kind of want to build upon that. So thanks especially for the inhalation products. As we said, the dissolution seems to be critical for certain things and there's multiple methods that have been shown to be sensitive. I did hear about the iBCS class. So the inhalation biopharmaceutics classification system that folks have been developing and I was curious. Maybe if Andrew and maybe Wenlei want to comment, is there potential? Is that something that, you know the industry sees as you know, very useful? And if so? Are there certain gaps, maybe in that system? That we could build towards to kind of build upon that, you know, dissolution being part of that as well as PK kind of like would that help us build that IVIVR we're looking for and are there you know potential areas that you know FDA should focus on and towards in terms of that, that idea that's been used in other dosage forms. So curious to hear any thoughts on that.

So, Wenlei. Yeah. What do you think we should invest more from research perspective? So do we need to go more standardized? The dissolution or biorelevant one from bioequivalence perspective.

Wenlei Jiang (FDA)
Yeah. Thank you for asking me this question. I think I mean my perspective of bioequivalence, I think standardized dissolution method is important and also to me the, I guess we're looking for biorelevance, but I think many times very difficult. So I think that the bioequivalence perspective, the goal is to differentiate the formulation difference. I think I want to echo what Xiaoming said you want to look into your formulation, design, manufacture, process and then you validate if your dissolution method is discriminative. That can tell the difference, so that is what I'm in my perspective, it's a good combination. The balance between biorelevance and your design of the dissolution method.

Moderator
From from industry like, do you have any comment about the biorelevance challenges that you are finding developing the method?

Andrew Cooper (Viatris)

Could I first comment on the question about the iBCS classification, I think, I mean it's a fairly new concept. But it's been nicely laid out in stages and it's really only in this current paper that that, that people have started to discuss the application of that classification in certain circumstances, including bioequivalence. And I think what we see is, is maybe similar to what happened with oral BCS 20 years ago or so you know that it actually takes time to really work through the consequences, because what a BCS classification doesn't do is tell you the answer to every question. What it does is provide a rational framework for thinking about what the answer to those questions might be.

And I think that does take time. It takes time as you apply that thinking to different cases. To work that through. What could the agency do to help? Well, some of the there are some gaps identified, I think, within that within that paper and there are some pretty fundamental gaps and I know we've actually talked about one of them today or at least alluded to one of them today, which is around the availability of relevant permeability data is pretty limited and there are some real challenges with kind of in vitro based assessment of permeability, perhaps particularly for the Class 3 type molecules which slip between the kind of membranes rather than going through the cells, and so, you know, there are some, there are some challenges there and there's not really such a clear framework. Even solubility measurement is challenging for very low solubility compounds.

So there are some fundamentals there that that need some work, but I think the other thing is just to look for opportunities to kind of validate the thinking and say, well, OK. What this classification suggests is this. But what data can we then? What data can we generate? To improve on that and can I just make one comment on dissolution? I think I largely agree with entirely what's been said so far, actually, that I think that that sometimes the method which is most predictive is not, which is most biopredictive, is not necessarily the method which is most exquisitely biomimetic.

As you might say, because biomimetic methods often tend to focus on one aspect of the in vivo situation. I mean, in doing so, they tend to make compromises around particularly the ability to make robust measurements and maybe miss out or misrepresent other aspects. And so I suspect that in many cases the most biopredictive methodology will turn out to be the methodology which best actually detects the fundamental physical chemical differences between things and it's, I mean, in the world of generics, it's all about difference and it's about discrimination for difference. And I think really when you when you measure accurately the physical chemical fundamentals, it's those fundamentals that ultimately are playing out in the in vivo system and so that's certainly my preference in approaching any measurement really to start with something that captures the fundamentals well.

Moderator
I think it may not be fair to separate biorelevance from bioprediction here, especially for inhalation systems or inhalation. I would say medication when the dissolution is happening. We have a deposition and we are choosing to use realistic aerodynamic particle size distribution as an input for the solution in this case so. So I would say still this area needs research efforts to synchronize between the deposition in in a parallel way and how the dissolution rate can affect the permeation and availability either for local action or for systemic distribution. So with this I would say like if there is no any comment from industry or FDA.

Wenlei Jiang (FDA)
Actually I want to comment on the dissolution methods for the inhalation product. Today we talk a lot about the dissolution methods, but I also want to kind of clarify. We probably need to

differentiate dissolution method for quality testing and dissolution for bioequivalence demonstration. I think for the dissolution method for quality testing we really need to standardize them. For example, the selection of the dissolution media. It may not be relevant. But it has to produce consistent results.

So I think we probably need to clarify that also I want to address Elizabeth's question regarding the iBCS concept. Yeah, this is I think a good concept for the inhalation product. We do see some of the immediate application. For example, if it's iBCS class one and three, maybe we don't really need implement the dissolution for those products, but I agree, we do need to collect more data to kind of make better use of this iBCS concept. For example the permeability parameters and FDA we also have some internal research to use, like lung-on-a-chip to measure the permeability of certain compounds, and we do encounter some challenges. For some of the very hydrophobic compounds it has like absorption on the system.

So actually insisting learning more about like Maxime you mentioned about some of the in vitro cell based permeability measurement you got for some of the model compounds, I think we really need to build a database to have some of the permeability data collected from different systems.

Hailing Zhang (FDA)
So I want to add a comment to Wenlei's comment in terms of the dissolution test for inhalation product. Probably people probably not aware where the biopharmaceutics division in OPQ. We are mainly review biopharmaceuticals in all the submissions in programs so including and people probably thinking we're the main division review dissolution as a control a quality control kind of approach. So for inhalation product, I think we see dissolution task being added to some of the PSGs recently, but I want to make it clear that we are not there yet to include dissolution tasks in as a control quality control task for inhalation product I want to make that clear? It's mainly for equivalency purpose and also probably in the future for the post approval changes purpose.

Moderator
Great things I think for time we can end it there. So getting great discussion for the panel. Thank you.