This transcript was assembled from Artificial Intelligence (AI) generated captions and may contain errors.

Session 3 –Future Horizons for Assessing the Bioequivalence of Complex Products: Challenges in the Next Five Years

Co-Moderators:
Bryan Newman, PhD Lead Pharmacologist, DTP I, ORS, OGD, CDER, FDA
Ahmed Zidan, PhD Senior Research Pharmacologist, DPQR V, OPQR, OPQ, CDER, FDA

- **Establishing Equivalence of TDS and OIDPs**
  Priyanka Ghosh, PhD Lead Pharmacologist, DTP I, ORS, OGD, CDER, FDA

- **FDA's Perspectives on Current Quality and Bioequivalence Challenges for Complex Products**
  Andre O'Reilly Beringhs, PhD Staff Fellow, DTP I, ORS, OGD, CDER, FDA
  Renishkumar Delvadia, PhD Senior Staff Fellow, DPQA VIII, OPQA II, OPQ, CDER, FDA

- **Challenges and Opportunities for Complex Generic Products**
  Brandon Wood, BSc Sr. Director, RA I & Combination Products Liaison, Teva Pharma USA, Inc.

- **Evolving Technologies Shaping New Research Needs for Future Pulmonary and Nasal Generics**
  Carla Vozone, PharmD, MBA Vice President Specialty Drug Delivery, Catalent Pharma Solutions

- **A Taxonomy for Categorizing User Interface Design in Medical Device Development: Human Factors Application, Development Opportunities, and Potential Integration of AI and Machine Learning**
  Megan Conrad, PhD Associate Professor of Mechanical Engineering, University of Detroit Mercy
  Mary Beth Privitera, MDes, PhD Professor, Biomedical Engineering, University of Cincinnati

- **Industry Insight: Clarity and Consistency for Complex Generics**
  Russell J. Rackley, PhD Global Head, Clinical Pharmacology, Viatris

Panel Discussion

In addition to moderators and presenters listed above:

FDA Panelists:
Robert Berendt, PhD Supervisory Chemist, DPQA V, OPQA I, OPQ, CDER, FDA
Andrew Clerman, MD, PhD Acting Lead Physician, DTP I, ORS, OGD, FDA
Lanyan (Lucy) Fang, PhD Deputy Division Director, DQMM, ORS, OGD, CDER, FDA
Bing Li, PhD Expert Pharmacologist, Associate Director for Science, OB, OGD, CDER, FDA

Kimberly Witzmann, MD Deputy Director, OSCE, OGD, CDER, FDA
Rob Lionberger, PhD Director, ORS, OGD, CDER, FDA

Closing Remarks for Day 1

Ahmed Zidan, PhD

Moderator

Hello. We're going to start again, so please have a seat. Before we start the session, there is an announcement. We have found a cell phone with a blue case. I think somebody has lost their phone, so we've kept it at the registration desk outside. If you've lost your phone, you can go there and check it.

Welcome again to our third session of our workshop. The title of our session is "Talking About the Future: Future Horizons for Assessing the Bioequivalence of Complex Products and Anticipated Challenges in the Coming Five Years."

I am Ahmed Zidan, and I am a senior research pharmacologist at the Division of Product Quality Research 5 within the Office of Product Quality. I am pleased to moderate this session with my colleague Dr. Bryan Newman. He is the lead pharmacologist and team lead at the Division of Performance One at the Office of Research and Standards of OGD.

This session will mainly highlight the anticipated challenges and opportunities for the assessment of bioequivalence and quality for complex products over the next several years. The topics we are going to cover will include the need for and design of in vivo studies, FDA's perspective on current and future quality and bioequivalency challenges, the evolving complex product landscape, and the role of machine learning in device taxonomy and considerations around irritation studies for transdermal products.

We are going to have a total of six talks, two from FDA and four from industry, before our panel discussion. All the speakers' and panelists' bios are available on the conference web page; please refer to this if you need more information.

I would like to emphasize that the aim of our workshop is to solicit input on research priorities for the next year of GDUFA research. For all online attendees, if you have any questions, you can post them on the docket using the barcode in the corner here. For in-person attendees, if you have any questions, we can wait until the panel discussion to address them.

With that said, we'd like to invite our first speaker, Dr. Priyanka Ghosh. Dr. Ghosh will give her presentation on establishing equivalence of transdermal and oral inhalation drug products. Dr. Ghosh is a lead pharmacologist in the Division of Therapeutic Performance I, Office of Research and Standards of OGD. Please welcome Dr. Ghosh.

Priyanka Ghosh (FDA)
Thank you, Dr. Zidan.

I'm going to talk very briefly on two quite unrelated topics. What we really want to do with this presentation is get your thoughts on whether these research topics are of interest to industry and, if so, what kind of specific research or studies we should do over the next few years.

I'm going to start with transdermal and topical delivery systems. These are systems where you adhere the product to the skin, and they typically deliver the drug into the systemic circulation. For these products, in the product-specific guidances, we typically recommend a PK study to assess the performance. We also recommend adhesion, irritation, and sensitization studies. Since these products are considered drug-device combination products, we also have recommendations related to the device characteristics in the PSG pages.

These product-specific guidances are supported by general guidances which discuss the quality recommendations related to these products, as well as the performance recommendations, specifically related to transdermal adhesion and irritation and sensitization studies. The general guidance on adhesion recommends a comparative study evaluating the adhesion performance of the generic product and the reference product in vivo in humans. Based on input we have received at previous GDUFA research meetings, we have also initiated research projects to look at whether in vitro models can be used to further derisk product development as it relates to transdermal adhesion.

For the irritation and sensitization studies, our guidances currently recommend comparative in vivo studies evaluating the irritation and sensitization potential of each generic product compared to the RLD to support submission and approval of an ANDA. The general guidance goes on to recommend very specifically the evaluation of irritation and sensitization potential under provocative conditions, which is basically a 21-day study with repeated applications of these products to see if any of the active or inactive components in that drug product are more irritating or sensitizing compared to the reference product. The guidance does state that in some situations, a sensitization study may not be needed.

What we have done internally is look at all ANDAs that have been submitted and approved between 2012 and 2022. This encompassed a wide variety of active ingredients, as you can see here on the left, and also a wide variety of inactive ingredients. Just to remind you, the major reason for recommending these irritation and sensitization studies was under the principle that different combinations of active and inactive ingredients, because these products are not required to be Q1Q2, could elicit an irritation and sensitization reaction that is different compared to the reference product. We wanted to utilize these studies to be able to evaluate the irritation and sensitization potential.

Looking at all these ANDAs that have been approved over the last decade, we had about 30 approvals during this time. The way we presented the data on this slide is what happened to the applications when we first received the studies. I would like to remind everybody that all these ANDAs ultimately supported both the irritation and sensitization studies and were found to be acceptable for these products.

When it comes to sensitization, we found that there was just one situation where the sensitization study was not found to be adequate based on the first cycle of review. Eventually, as we know, the study was for methylphenidate, and we know that the API is sensitizing, so now our product-specific guidance for the methylphenidate transdermal system no longer recommends an evaluation of the sensitization potential of a prospective generic product.

When it comes to irritation, we found that there were about four out of these thirty instances where the studies were not found to be adequate during the first cycle of review. But what the investigation also revealed is that these study failures during the first cycle of review were not related to the actual formulation or the composition of the product, but more related to the study designs that were used at that point in time. Of course, there were successful studies that were eventually conducted to support the approval of all these products.

So the question we have for you is: Are there studies that are now being conducted or can be used to further de-risk product development, so that we may not need in vivo irritation and sensitization studies for every single generic product in the future? We definitely would like to understand from you if this is an area of interest and if there are things that are already being done or can be done to streamline product development in the future.

Switching gears now, I'm going to briefly talk about orally inhaled drug products. There were a lot of talks this afternoon on this topic, so I'm going to go over the first couple of slides very quickly. As we've heard from previous presentations, over the last few years, as an alternative to the comparative clinical endpoint studies, we have these more efficient BE approaches in our guidances. They have criteria for formulation, physical-chemical characterization criteria, and for all these products, they recommend a PK BE study. For a subset of these products, an in vivo PK BE study with a charcoal block is also recommended.

The PSGs also encompass recommendations for devices and options for computational modeling approaches. Now, these charcoal block PK BE studies are primarily recommended because a portion of the emitted dose from these OIDPs could be swallowed rather than being inhaled, and for some drug products where this gut absorption component can be significant, these charcoal block studies really help to assess what component of that systemic dose was from lung absorption compared to GI absorption.

As I mentioned, and as was mentioned in other presentations as well, these studies are only recommended in a subset of our PSGs where the API has significant gut absorption. In those PSGs, there is a very high-level recommendation at the moment about the study design, which says the study should be done in healthy subjects with the minimum number of inhalations that is required to characterize the PK profile. It also states that multiple doses may be needed in some cases. The most important thing here is that the guidances say that the charcoal dose should be justified.

Because the recommendations are a little bit high-level at the moment, one recommendation we have for all of you is if you are considering conducting these charcoal block PK BE studies as part of your overall BE approaches, we strongly encourage you to discuss your study design as well as your potential alternative approaches to the charcoal block PK study with the agency prior to conducting these extensive in vivo studies.

The questions we have for you today are threefold. The first is related to the recommendations we have for charcoal block studies in the PSGs. They are high-level, and there are outstanding questions that we have identified, but there could be additional questions that you have identified. We really want to narrow down the scope of research that we may want to explore in this area.

So the first question is related to the dose. We kind of know the dose of the drug product that is used in these studies, but what we want to ascertain is what is the appropriate dose of the charcoal block and if more than one dose needs to be administered to have a successful outcome in this study. And most importantly, what methodologies can be used to determine that dose prior to going into this "pivotal" BE study with charcoal block?

The second question is, there is some information in the literature about when charcoal block studies and what dosing should be for the charcoal block itself during the study. However, there are open questions related to how often charcoal should be dosed during a PK BE study. What are the optimal times, and can this be generalized across drug products? Or do you have to identify both the dose as well as the optimal time for dosing for each product separately?

The last question that we have identified is, are there alternative approaches available? For example, partial AUC-based approaches or modeling and simulation-based approaches that can be used to basically address the same question that the charcoal block study is designed to

address at the moment? If yes, do we have the tools in place, or do we need additional research? Do we need further development of the modeling and simulation tools to be able to use those as an alternative to the charcoal block studies?

So these are the two questions we have for you this afternoon. With that, I would like to thank everybody who contributed to the preparation of this talk as well as our entire team within the generic drug program. Thank you.

Moderator
Thank you, Priyanka.

Our next talk is really a unique talk. As we know, quality and bioequivalence are just two sides of the same coin; it's all about characterizing the drug product. For this, we're going to have a talk on FDA's perspective on the current quality and bioequivalency challenges for complex products. Our speakers are Andre O'Reilly Beringhs, who is a staff fellow in DTPI, ORS of OGD, and Renishkumar Delvadia, who is a senior staff fellow in DPQA VIII and OPQA II in OPQ of CDER.

Andre O'Reilly Beringhs (FDA)
Thank you so much, Dr. Zidan, and good afternoon, everybody. My name is Dr. Beringhs, and on behalf of myself as well as my colleague Dr. Delvadia, I will present today a brief 10-minute, fast-paced overview of FDA's perspectives on bioequivalence and quality challenges across a range of dosage forms and routes of administration. This is a really high-level presentation, and the goal here today is to expose you, the audience, to a variety of challenges that we have been facing so we can receive your feedback via the public docket.

We would like to hear from you if you have research ideas or potential suggestions on how FDA could address these challenges. Last but not least, we would like to entice you to raise your interest in collaborating with FDA via a variety of mechanisms in order to help us resolve these challenges.

Now, before we dive into today's unresolved questions, I do want to take a little bit of time to emphasize why this conversation is important. The reason for that is because GDUFA-driven breakthroughs have essentially paved the way to complex ANDA approvals. Taking a look at the data from the previous fiscal year, as you can see, about 20% of all ANDA approvals have been impacted by GDUFA science.

Looking at the absolute number of ANDA approvals, that is an average of around 160 every year over the past five years. That would simply not be possible or would be substantially delayed if it wasn't for GDUFA research outcomes. A few notable examples here could be the budesonide inhaler, in which GDUFA research reduced the need for clinical endpoint bioequivalence studies; the case for naltrexone for extended-release injectable suspension, in which GDUFA research has enabled alternative methods to support drug product sameness; cyclosporine ophthalmic emulsion, in which GDUFA research helped us develop a Q1/Q2/Q3 microstructure fingerprinting approach in lieu of in vivo trials.

So ultimately, the takeaway here is quite straightforward: GDUFA regulatory science investments do pay tangible dividends in faster, lower-cost approvals, especially for complex generic products.

Now, keeping that in mind, we're going to start going through different routes of administration to discuss current challenges that we face, and we would like you to continue thinking about which of these topics will be most important to you for us to invest our time and resources in moving forward.

In terms of topical semi-solids, IVPG has historically been a challenge, but FDA has put a lot of effort and time towards that. Nowadays, we do feel like there is quite a substantial amount of information out there regarding the science and standards, as well as expectations behind comparative IVPG studies. But we do welcome any potential feedback or comments that you may have via the public docket regarding this topic.

Now the second aspect on topical semi-solids is Q3 assessments for products with compositional differences, and this goes towards the talk Dr. Walenga gave earlier today, and he very nicely covered that. There is great interest in understanding when Q1Q3 assessment for topical semi-solids that are compositionally different can be reasonable and justifiable in order for us to be able to determine a Q3 sameness for this class of products. Now, considering that, we do think integrative modeling could play a critical role here.

However, there are challenges there. Model validation and implementation are still unclear for topical dermatological products, and that reflects on the fact that we currently do not have model-only BE approaches recommended in PSGs for this class of products. So we would like to continue exploring totality of evidence approaches by Q3 that combine modeling for these products.

Now in terms of transdermal and topical delivery systems, I refer you to the presentation that was just given by Dr. Ghosh. There is overall a lack of biorelevant in vitro adhesion tests, and we would like to better understand when skin irritation and sensitization tests are truly needed for this class of products. So for that purpose, we also would like to continue exploring the potential use of systematic adhesion tests.

Moving forward to inhalation and nasal products, in terms of dry powder inhalers, these products have typically suffered from high inter-batch variability, and there is an overall lack of understanding between the particle and aerosol performance connection for these products. We would like to continue exploring high-resolution morphology mapping technologies associated with deconvolution studies that could provide us a better understanding of where these variabilities come from, both in an in vitro setting as well as an in vivo setting.

For metered-dose inhalers and next-generation propellants, regarding challenges, there is a lot of variability when it comes to spray and aerodynamic particle size distribution characteristics. With the implementation of new propellants, we would like to better understand when these differences are important or not for us to set an appropriate BE framework that makes the replacement or substitution of these propellants easier and more streamlined. We think formulation-device interaction studies could be important, leveraging PBPK and in vitro and in silico models to achieve that.

For nasal and nose-to-brain products, there's currently no validated regional deposition model that we could use, and when it comes to the central nervous system, these models also tend to not account for that in terms of the delivery target site. We would like to invest in the development of 3D nasal models that have capabilities of providing deposition readouts, and we would also like to develop surrogate endpoints for central nervous system-acting drugs, especially those nose-to-brain drugs.

Now moving forward to complex injectables, in terms of in situ forming depot, there is a need for developing validated in vitro models that can describe depot formation and the impact of formulation differences on that depot formation, and also models that can account for high variability from injection factors and can evaluate the potential impact of those variabilities from the administration procedure. So for this purpose, we would like to continue investigating injectability rigs with high-resolution imaging capabilities that can provide that kind of understanding, as well as combine that with physiologically relevant dissolution models.

In the realm of nanoparticle-based injectables, we're particularly interested in unbound and bound nanoparticles at this time. We would like to further investigate the impact of unbound stabilizers on nanoparticle bioequivalence and quality. For this purpose, we do think profiling the stabilizer levels of these products on the market could be an interesting approach in order for us to develop a risk assessment framework for stabilizer differences in this class of products.

In terms of Q1/Q2 flexibilities for parenteral route, we would like to continue investigating the potential impact of minor formulation differences on bioequivalence and quality of these products. The ultimate goal here will be to combine Q3/Q4 fingerprinting as well as PBPK modeling in order to develop science-based safe harbor justifications for formulation variations.

Moving into ophthalmic products, for intraocular implants, there is a need to predict long-term ocular PK for these products as well as start developing structure-release relationships. We would like to continue exploring modular toolkits for this purpose, as well as combining PBPK modeling.

For posterior segment depot products, we would like to further understand what is the potential impact of Q1/Q2 and Q3 differences on the product performance of these vitreous depot products upon administration. We would like to invest in the development of vitreous mimic chamber models that can leverage in vitro-in vivo correlations.

Now another very interesting topic for ophthalmic products is permissible excipient differences. Also another topic that has been discussed here today. We would like to further understand what is the potential impact of Q1/Q2 differences for ophthalmic products that may not necessarily require an in vivo bioequivalency study to support those differences, and we would like to understand what would be reasonable equivalents to BE criteria for exceptional excipients for this route of administration. We think we could accomplish that by leveraging AI-based Q3 fingerprinting approaches that combine in vivo as well as ex vivo ocular data.

In the realm of otic suspensions and gels, one of the main challenges that we have seen is that it's really complicated to evaluate these products, especially when they have formulation differences. So we would like to develop better models that can allow us to understand the potential differences, particularly in middle ear permeability for these products. One exploratory idea here would be the development of a tympanic organ-on-a-chip system that can provide real-time permeation data and that could be leveraged for pharmacokinetic prediction approaches.

Now moving into peptide and oligonucleotide products, also another topic that has been thoroughly covered today, I have here a few additional points to consider. In terms of oral and nasal peptides, there is a need for in vitro models that can account for enhancer-driven absorption in a reliable manner and that can also account for mucosal dynamics. So here we

would like to continue investing in epithelial perfusion models that have capabilities of tracking in real-time proteases as well as enhancers.

In the realm of depot-forming peptides, we would like to develop tools that can model long-acting pharmacokinetics for these products and we would like to establish depot structure and pharmacokinetic connections. We think depot shrinkage imaging approaches as well as subcutaneous release modeling could be an approach here that could provide substantial information.

Now in terms of oligonucleotide impurity characterization, this has been one of the main challenges, particularly in terms of sensitivity and resolution. So we would like to continue investing in orthogonal techniques that can allow us to conduct impurity profiling of these products for low-level process and sequencing-related impurities, and we would like to develop a better understanding of what will be the potential off-target and immunogenicity risks for this class of products when differences in impurities exist.

Last but not least, the final topic that I would like to mention today is AI tools applied to complex generics. We have an interest in investing in AI tools for four particular purposes:

The first one is on predictive BE modeling across different routes. We think a PBPK-AI hybrid model that is trained on clinical as well as in vitro data could help FDA define what is a clinically informed meaningful difference in product characteristics, which could eventually support waiver requests of in vivo bioequivalence studies for complex generics.

In terms of excipient forecasting, we think AI-guided approaches could help us better understand the potential impact of these formulation differences and support safe harbor justifications for Q1/Q2 flexibilities in these products.

Immunogenicity screening could help us. LLMs could help us derisk these oligonucleotide and peptide submissions.

And lastly, in review streamlining, we think AI could be a great tool to help us flag early challenges during submission review as well as enhance first-cycle approval rates.

With that being said, I hope you all heard the call to action today. This was a very broad presentation, so we hope to hear from you in the public docket on your priorities and what you feel like we should be emphasizing in our future research from now on. And I do encourage anyone interested in collaborating with FDA for research purposes to visit our Generic Drug Science and Research website that is on your screen where you can find more information regarding funding opportunities for research projects.

With that, thank you very much.

Moderator
Thank you, Andre and Ranesh, for the wonderful presentation.

Our next talk is an industry talk. So we can move to Brandon Wood. Brandon is the Senior Director of Regulatory Affairs and Combination Product Liaison at Teva Pharmaceuticals USA, and Brandon is going to talk to us today about challenges and opportunities for complex generic products.

Brandon Wood (Teva)
Thank you, Dr. Zidan.

Good afternoon, everybody. I was starting to prepare to say good evening, but kudos to the workshop coordinators for mostly getting us back on track. My name is Brandon Wood. As mentioned, I'm presenting on challenges and opportunities for complex generic products. The opinions expressed in this presentation are mine and not necessarily those of Teva Pharmaceuticals.

In terms of presentation contents, first we'll talk about GDUFA-funded research from a regulatory perspective. I have several topics on bioequivalence, characterization and demonstration of sameness, immunogenicity research, and the missing link. The propellant transition for metered-dose inhalers and we'll wrap up with some parting thoughts and acknowledgements.It's a bit of a potpourri of complex challenges.
I also like to start presentations with more of a level set. You know, why are we here? What are we doing? Well, why are we here today? We're here to provide public input to help FDA identify science research priorities that can help expand and accelerate patient access to generic drug products. The whole point is to expand and accelerate patient access to generic drug products. We're also here to find ways to lower generic drug development costs and time without sacrificing quality, safety, or efficacy. We're also here in acknowledgement of the importance of increasing the availability of FDA-approved cGMP-compliant complex generic drugs that can lower healthcare spending both by payers and patients.

Why are these research and science priorities important? These priority areas encompass scientific challenges that both the industry and FDA generic drug program identify as being significant over the coming years. They also represent opportunities for scientific advancements, again to accelerate access to generic versions of complex products and make the development of generic drugs more efficient.

So then you have to ask yourself, is the GDUFA science and research program helping? Is it actually helping with accelerating access to generic versions of complex products and making the development of generic drugs more efficient? And the answer from an industry perspective resoundingly is yes, absolutely. But there's still certainly work to do, as can be seen all throughout the workshop today.

The realizations of this program, whether it's PSGs, guidances, scientific articles, posters, you name it, these are all vital to a generic ecosystem that can navigate today's challenges but also anticipate and adapt to tomorrow's challenges. So as technology and new drugs continue to advance in complexity, the regulatory research program must enable flexible, scientifically sound regulatory approaches.

So with that, we'll jump into our first topic on bioequivalence. And this specifically is related to long-term use, complex products and extension of wear. The challenge is that some products, such as hormonal contraceptives, have long-term usage, multiple years. PK studies can be abbreviated in less than the duration of wear. However, innovators sometimes will extend their usage duration by several years. The development of generics is very time-consuming and expensive. Industry needs assurance that the BE requirements are not changed as the innovator extends usage by multiple years.

To the right of the slide, I've provided some PSG snapshots where you can see that the intended period of product use is a consideration of the PSG and the recommendations for the

agency to evaluate whether the current BE recommendations in PSGs account for potential changes in the duration of usage by the innovator, so that either our future ongoing or completed costly bioequivalence studies could support such a change.

One potential consideration would be to tighten the bioequivalence criteria instead of changing the study design or the duration of study, which could become problematic for those with studies already completed or conducted.

Next, this has just been referenced: charcoal block PK studies for inhalation products. FDA has recently incorporated these studies for inhalation products. As you can see in the PSG snapshots to the right, however, there's no standardization of the amount of charcoal needed and the timings of its administration in these studies to ensure sufficient block of the GI absorption.

In terms of recommended research, similar to fed studies with a high-fat breakfast with a specific range of calories for protein, fat, and carbohydrates are recommended by guidance. And FDA also has a standard high-fat breakfast with predetermined foods. It would be beneficial to answer your question, Priyanka, to have a standardized approach to charcoal block PK studies with respect to the amount of charcoal needed and the time points to administer. The charcoal research may include in vitro charcoal absorption studies or in vivo bioavailability studies. Standardize this not for single products, but possibly for larger groups of products such as inhalation products.

Next is uncertainty regarding the number of inhalations to use for inhalation PK studies. PSGs for inhalation products specify a dose as you can see, to the right of the slide, "a minimum number of inhalations that is sufficient to characterize the PK profiles by using a sensitive analytical method" instead of an exact dose like oral products. Some oral tablet and capsule PSGs specify the number of units to dose due to low concentrations. And some oral suspension PSGs specify the volume of suspension to dose. So as a consideration when creating or revising PSGs, FDA should specifically indicate the recommended dose to support inhalation PK studies to alleviate residual uncertainties in these complex products.

And the last topic on bioequivalence is related to PSGs for oncologic and/or pediatric products. The challenge is that there are PSGs for oncologic and/or pediatric drugs where dosing and administration according to the prescribing information must be followed. You can see some snapshots to the right of the slide. However, in reality, recruiting very sick patients or children who need to adhere to multiple dosing cycles and extensive PK sampling is very difficult to achieve. Also, orphan drugs having a low incidence rate of the underlying condition are also particularly challenging. Again, in reality, there are very high dropout rates for these types of studies and in general low motivation for patients to enroll in generic PK studies.

So in terms of recommended research, PSGs for these very specific types of drugs for oncologic and/or pediatric drugs, the agency should anticipate the different circumstances and challenges that these specific patient populations introduce. To alleviate the difficulties and residual risk of conducting these studies, in vitro and/or model-based research approaches should be clearly defined in the PSGs instead of proposing general concepts without specific details.

Switching gears to characterization and demonstration of sameness. This is related to analytical methodology. The challenge is that there are several advanced analytical techniques that are required to demonstrate API sameness and comparable physical-chemical attributes. As

recommended in PSGs for complex products, you can see to the right some recommendations for peptide, oligo, and iron reference listed drugs. FDA has broad discretion to determine whether an ANDA applicant has submitted information sufficient for the agency to reasonably conclude that the proposed generic active ingredient is the same as the active ingredient of the RLD.

What we've seen, what industry has seen is that the agency has specific preferences on sample preparation, study design, etc. But these preferences are not documented in guidance and are only learned in deficiency letters. And unfortunately in some cases it's the second or third deficiency letter which is not efficient to anyone involved.

In terms of recommendation, the recommendation is to conduct research to develop a guidance or position with recommended sample preparation, study design, etc. for the more common advanced analytical techniques based on product type such as peptide, iron, complex oligonucleotide.

Next is for statistical analysis. Statistical analyses are sometimes employed in data evaluation to demonstrate sameness and answer the very difficult question of how close is close enough. There are no FDA guidances on preferred statistical techniques, creating residual uncertainty in whether the results will be considered acceptable. And often industry defaults to the population bioequivalence approach because this is most commonly accepted by FDA. I provided a specific example to the right, but it's acknowledging statistical evaluation of similarity for peptides and oligonucleotides using NMR spectroscopy. But in terms of recommendations similar to the previous slide, the recommendation is to conduct research to develop a guidance or position with recommended statistical approaches for various physical-chemical comparisons based on product types, again such as peptide, iron, complex oligo, etc.

Moving to immunogenicity, this is specifically related to adaptive immunogenicity research and the challenge is that there are two initiatives that are happening in parallel. USP granted a contract to create an immunogenicity standard for adaptive immunogenicity, which really will work well on their specific assay platform. And there's a separate initiative by APS and HESI wherein they examined adaptive immunogenicity assays across multiple innovator labs and their results suggest that adaptive immunogenicity assays can vary widely in the results by format.

And a specific example in the research performed by - presented rather by Laurent Meunier at the 2024 Immunogenicity Summit - a sizable known to be immunogenic in clinical testing was observed to be immunogenic in many platforms but not all. Additional work is ongoing to determine if this is a limitation of certain assay platforms or could it be that different platforms provide different information? And how might this information impact in vitro approaches for generic peptide and oligo assessment?

As a recommendation, FDA should organize a consortium for testing of any standards produced to ensure compatibility with multiple adaptive immunogenicity assay formats and to better understand the differences between the formats.

The last immunogenicity topic was cleverly coined "the missing link" by my colleague Andrew Graves. But the challenge is that in vitro immunogenicity assays are used - clearly as has been discussed throughout the day - to support ANDAs for generic peptides and oligos as clinical trial testing for safety and efficacy are not suitable for the 505(j) ANDA pathway. However, the in vitro

testing provided provides risk assessment that may or may not be relevant to the clinical experience as the clinical relevance of these in vitro assays has not been established.

As a specific example, while an impurity in a proposed drug candidate may exhibit a statistically significant increase in immunogenicity compared to the reference product, it's not clear if the same increase is in any way biologically relevant without further research. Generic developers are limited in their options if they observe any type of statistically significant difference in in vitro immunogenicity. As a recommendation for potential research, a grand sample testing in a phase one or phase two clinical study could potentially compare immunogenicity from in vitro samples collected prior to dosing patients with a product or placebo to the clinically relevant observations for safety, efficacy and immunogenicity observed in those same patients after dosing to establish a correlation. This could potentially provide an additional tool when there are statistically significant differences in data in vitro that are observed.

The last topic is related to the propellant transition and here through the Kigali amendment to the Montreal Protocol, there's a global phase-down of the second-generation metered-dose inhaler propellants, HFC-134a and HFC-227ea. Propellants are critical drivers of MDI performance as they release the drug from the actuator, facilitate the atomization of the formulation into aerosolized droplets, and maturation of the droplets to their depositing forms. And also constitute the bulk of an MDI's formulation.

In response to the global phase-down, companies are in the process of transitioning to 3rd generation propellants, HFC-152a and HFO-1234ze. But there's a lack of clarity on the regulatory requirements to transition to a new propellant, and research is needed to facilitate a smooth transition and, more importantly, uninterrupted access to patients with these critical medicines.

Here we need to take a lesson from history. The first-generation propellants, chlorofluorocarbons (CFCs) were phased out in response to the Montreal Protocol, but the removal of CFC propellants was complex. It's multifaceted and it was a multi-year process that negatively impacted the availability of generic MDIs. Surely we can learn from the first transition to minimize or eliminate the impact this propellant transition will have on patients who rely on these important lifesaving disease-treating medications.

In terms of recommended research, FDA should evaluate whether abbreviated in vitro and/or in vivo bioequivalence packages could be utilized to support a transition to a third-generation propellant. The research focus on the extension of the "Option 1" bioequivalence approach as recently updated for locally acting products to include the new propellant so long as a weight of evidence is provided, indicating that the product performs comparably both in vitro and during systemic absorption studies.

Just to share some parting thoughts here. The GDUFA Science and Research program is a critical factor in the generic ecosystem, and the outputs represent opportunities for scientific advancements to accelerate access to generic versions of complex products and make the development of generic drugs more efficient. A continuous feedback loop and meaningful industry-agency collaboration such as this workshop will streamline the utility of the research performed. And focus should be put on ensuring that the research performed is compatible, useful, and reproducible for generic applicants to incorporate into development programs in a timely manner.

To quote Henry Ford, "Coming together is a beginning, keeping together is progress, but working together is success."

OK. And I'd be remiss to not give a sincere note of acknowledgement to Craig Trexler, Lucia Vuletic, Andrea Rosman, Andrew Graves, Claire Butler and Aaron Josephson. Without your contributions, this presentation would not have been possible.

So with that, I thank you for your time and look forward to the panel discussion.

Thank you.

Moderator
Thank you, Brandon for the insightful talk. So we can move to the second talk from industry by Dr. Carla Vozone. Carla is the Vice President of Specialty Drug Delivery at Catalent Pharma Solutions, and today, Carla is going to talk to us about evolving technologies shaping new research needs for future pulmonary and nasal generics.

Carla Vozone (Catalent)
Thank you so much, Ahmed. I had the opportunity to participate in the first GDUFA, the GDUFA I negotiations and be part of the first set of priorities, and I really wanted to recognize the FDA and appreciate all the effort. It's really remarkable to see the progress and the access to complex generics.

And today, thank you for the invitation to speak about the future. My presentation is a bit different. It's really looking at the pipeline of the industry currently in pulmonary and nasal drugs, just to inform about future research needs. And these views and opinions are mine and not necessarily those of Catalent.

So in terms of what I'm going to cover, it's the evolving landscape that we see in the nasal and pulmonary pipeline, the new delivery platforms, and I will focus on dry powder for inhalation because this is an area of expertise at Catalent. The advancing device systems and the new therapeutic modalities, and really bringing together some thoughts on potential research in the future.

So, you know, really in the last, maybe 10 years there's been really a resurgence in the pipeline of orally inhaled and nasal drugs. It has been growing at about 8% a year and is almost reaching 500 molecules in development and all of them are in pre-clinical, so you can see that there is a lot of dynamic involvement in the industry.

And you can also see that the innovation is driven to biologics and new modalities. So 40% of the preclinical programs are biologics and 50 to 60% are new modalities.

In terms of the therapies, so maybe when GDUFA started, most of the drugs approved were for respiratory conditions for asthma and COPD. That is going to be a very different reality in the future. 60 to 70% of the programs in development are for non-respiratory therapeutic targets, 20% are for CNS therapies and 55% for anti-infectives.

And seeing, you know, from a delivery standpoint, we can see that the nasals have really taken an important place in the last 10 years and they represent 40% of all the inhalation portfolio pipeline right now. And the nebulization is also increasing substantially. It represents 20%.

You know the MDIs that were probably, you know, so important and they remain important, especially with the propellant changes. But if we look at the pipeline of innovative drugs, they only represent 2%. So this is this is a kind of a device system that seems to be not so used for the future molecules in development.

In terms of what's already indicated, large molecules and when I say large molecules, it's really different biomodalities, so it could be nucleic acids, it could be other molecules that are not necessarily large molecules. They are all in this graph at the bottom.

And so you have here the breakdown on the application of the molecule. So in small molecules you see the neurological applications again, the anti-infective and and large molecules, the same with vaccines and immunostimulants taking an important percentage of the development.

And this is a timeline and it cannot have all the examples of disruptive technologies selected. Some that are related to dry powder for inhalation technologies and also with nasals and you see like in the last 30 years, 30 years ago there would be maybe every five years we would have a new medicine that would really bring a perspective, you know, like the first biologic with Pulmozyme or the first vaccine delivered by nasal, but now in the last 10 years the innovation is accelerating and almost every year you have another molecule. We have another product that will bring something different like nasal powders or nasal for emergency purposes or different API platforms that deliver insulin or deliver systemic drugs.

So this is just an example, our innovation is accelerating.

And going a little, you know, deeper on the dry powders for inhalation? The picture on the left is what has been more frequently or all the products in the market. They are based on lactose carrier-based blends. This is where lactose serves as a carrier of small API that is micronized and crystalline. And that has been the research or that has been shaping the GDUFA research has been very much connected with this lactose carrier-based formulations.

The new products and there are already products in the market I'll show in the next slide, but it's evolving to spray-dried powders. They are carrier-free and they are totally different from an excipient standpoint. This is a combination of excipients that will stabilize an amorphous form of the API. And all that particle is inhaled. So it is a totally different technology even though the framework of the research or it's kind of shaping product specific guidance recommendations that were developed for one and are not necessarily applicable for the other case especially when they are for systemic diseases, instead of locally acting diseases.

Now this is some photos and all these photos are from literature. They are not developed by us, but you can see how different the shape is. So when you have these sophisticated particle engineered technologies. And they are different ones. You can have like in the case of TOBI, you can have PulmoSphere which is based on porous spray drying particles. Or in the case of Inbrija the ARCUS spheres, they are larger in geometric size, but they are poorly dense, they are not very dense. So the aerodynamic particle size is achieved even though geometrically they are bigger. But you also have spray-dried particles that are the answer.

So really the morphology, the morphology is different from when you think about lactose-based API. And for many of these diseases, they are for systemic diseases. They are for where the drug that is in the blood circulation, that's what is going to determine clinical efficacy. So that aspect of morphology also has a different impact. As you think about the impact, the clinical relevance of the particle morphology.

Other that are non-spray-dried? Maybe they are less frequent but there are lyophilized powders also for inhalation purposes, there has been a trend in nasal powders. Some of them use spray drying. Other technologies like clarification as well. So the nasal powder aspect is another one that requires attention and future research.

And then other technologies like print, print is more recent technology.

Just to bring changing the topic here for device systems and I really wanted to bring the example of the aqueous aerosol because we see in the industry a lot of innovation around devices. And the reason is as you saw that first chart that I presented that nebulization was a significant part because it enables delivery of peptides. And it enables the delivery of all of nucleic acids that are not possible to deliver with other ways, because they would be degraded through so.

The aqueous aerosol delivery, the devices have been changing in mechanisms to be able to stabilize the delivery of those drugs. So while in the past there were more jet-based, you see vibrating mesh. You see ultrasonic mechanisms in development and also soft mist is quite a new system that is in development to deliver drugs. Aqueous-based drugs.

So I think what I wanted to bring to the attention of the potential research is to understand all the device options. Because when there are direct device combinations that are associated with a certain drug and it is too restrictive about the use of the device it basically blocks access to the industry to develop it creates barriers to the development potential. So there should be a research to understand what is an equivalent device with our devices that could be alternative and still achieve the same clinical outcome.

So in the last point it is about the modalities. So this really shows the diversity of biomodalities and modalities that are in development for both nasals and pulmonary delivery. And while they have very different characteristics, profiles, sizes and while it is clear that small molecules or nucleic acids, they are under CDER, there are some of the molecules in development that they are clearly larger than the 900 Dalton. So they will fall proteins or virus or bacteria. They will fall into CBER.

So I you know, it indicates for the future. And these products are still in early development, so that there is time, but in the future we could see the biosimilars in inhalation and in nasal delivery and potentially you know some collaboration that or a permeation of the knowledge that was developing see there to see where to enable those inhalation biosimilars to the market.

So just to bring some recommendations, I think we discussed a lot about the Q1 and Q2 demonstration. I think when we look at the spray-dried materials which include different types of excipients and way more complex the Q1 and Q2 requirement for the spray-dried formulation will be a barrier to development. If it is already difficult in lactose-based formulation in a spray-dried formulation, really demonstrating the inactive ingredients sameness qualitatively and quantitatively will be challenging for the industry.

So it will be important to have qualification of new excipients. I think there is research that allow for some, let's say alternative of excipients that are qualified and allowed by but for the generic industry to utilize, that could simplify the development route.

Also, the concept of the device sameness, I think we discussed this several presentations about the concept of device sameness and the need to flexibilize that concept.

And yeah, as just to close maybe with the morning. We talk with the new drugs in nucleic acids and peptides, the immunogenicity aspects of they will be relevant for pulmonary delivery as well.

Thank you.

Moderator
Thank you so much. Thank you, Carla, for your talk.

So we can move gear a little bit to our device-oriented talk. So we welcome Megan Conrad as Associate Professor of Mechanical Engineering at University of Detroit Mercy, and also Mary Beth Privitera. And she's a Professor of Biomedical Engineering at University of Cincinnati, but unfortunately Mary couldn't join us today, so Megan will give her talk.
Megan Conrad (University of Detroit Mercy), and Mary Beth Privitera (University of Cincinnati)
So Megan, she is going to give a talk about a taxonomy for characterizing user interface design and medical device development, specifically human factor application development opportunities and potential integration for artificial intelligence and machine learning.

Thank you. Mary Beth wasn't able to make it at the last minute, so she sends her apologies, but she did contribute greatly to this presentation.

So again, we're changing gears a little bit and talking now about the human factors processes involved in the ANDA pathway. Specifically, I'm going to introduce a taxonomy that we use for identifying user interface design features.

So we're talking about any of those design features on the device component that you interact with. Maybe you touch or you use a mouthpiece or a lever or even buttons. Anything you sense, a click, any on-device labeling, and then discuss what research and development considerations are necessary to further improve and enhance this human factors process for ANDA submissions. I want to acknowledge that our entire research team is grateful for prior funding, FDA funding and collaborations with the Office of Generic Drugs.

So the human factors process for comparative analysis and related comparative use human factor studies has had a draft guidance out since 2017. This process again looks specifically at human factors processes with a goal of demonstrating interchangeability of the device. And if necessary, through a comparative use human factors study, the goal is that if the device is switched between a generic and an RLD in the pharmacy, the new device that's received by the patient is as intuitive to use as that device that they're used to using. And when we look at the process, it's really separated into two different components.

The comparative analysis is more of a traditional human factor study. A comparative threshold analysis where we're looking at direct comparisons of the physical device and the labeling on that device. With the goal of identifying on the proposed generic if there are no or minor design changes not really necessitating further data, or if other design changes which are more significant changes that may need additional data to prove the safety and interchangeability. When other design changes exist, the guidance suggests that a comparative use human factor study should be considered to gather that data to demonstrate the interchangeability.

Now we know that there are challenges for implementing these comparative use human factors studies. Early in our research journey, we talked to many individuals, human factors practitioners and industry representatives who had conducted these studies and we really found that there was a chance that they found some of the procedures challenging and unfamiliar in the human factors community.

And so we set out to kind of dig into the process a little bit more and identified that after conducting a product overview for your proposed generic and comparing that to the RLD, certainly the next step is doing that comparative analysis by task. The design comparison and labeling comparison are included in the guidance and our team would recommend also considering use risk, which we'll talk about a little bit later. The determination then can be made whether those minor or other design differences are present.

In the instance where there are other significant design differences, then the proposal needs to be made for what kind of data is necessary, that comparative use human factors study. If there's alternative human factors study or existing data that demonstrates the interchangeability of this design feature, that will lead to ultimately further data analysis and your final ANDA submission. It's a little bit more straightforward when no data is required and so again, we always recommend the pre- and post-submission so that there's some course communication and controlled correspondence with the agency.

But a big challenge here that we set out to address was how do we make this decision of what is a minor or other design difference? And so the challenge here was that the ANDA procedures lacked a common procedure or language for comparing user interface design features between the proposed generic and the RLD. And we set out to develop a standardized tool, our taxonomy, that identifies and our user interface design attributes of the proposed generic and we thought it was important to link these user interface elements to tasks.

And why did we feel that's important? It's because our user interface directly influences how we're interacting with the device and therefore the product delivery. We like to simplify things. So we think of a different product that's distributed. In the case of ketchup, I think we can agree that the ketchup is in fact substitutable and delivered in different types of containers. However, if I'm going through a drive-through, the type of distribution matters to me. I'd rather have a small packet than a gallon jug, right?

Similarly with our combination products, we can prove bioequivalence or equivalency in the drug product itself. But it gets much more complicated and the end goal and the consequences are more severe when we're looking at providing consistent dosages with much more complex tests involved and then also ultimately caring about our patient safety.

So how do we intend to identify these design attributes and link them to tasks? Taxonomies are one way that are used in science to organize subject-specific concepts and create a vocabulary of those concepts. So we set out to create this user interface designed taxonomy that created a taxonomy of both labeling and interaction points that can create those definitions.

We made a very high-level taxonomy that could be applied to any medical device where we identified the category, subcategories and descriptors with corresponding definitions for both every type and component of labeling we know of and every type and component of interaction point we know of. And we developed this by using literature, by conducting a literature review of product design attribute descriptions, published defined definitions, and then AAMI, ANSI and

HE75 design nomenclature. From there, our goal was to make it specific to combination products.

So we broke it down to on-device labeling and then those components of device features as interaction points on the device and what kind of feedback you get from the device, whether it's auditory, tactile, etc. And from here we could develop a systematic process for comparing our generics to the reference listed drug. Now we wanted again to link it specifically to task.

So here we see if we have a task analysis where we have specific tasks represented on the rows on this figure, such as open the mouthpiece, load the medicine, we can use those taxonomy definitions. And here it's very visual where we identify the different user interface design features as identified on the taxonomy that are associated with each specific task or subtask.

If we look at the columns, it's easy to visually see side by side. When those taxonomy cards, those user interface design features are the same between products or different. Now, the reason why we're interested in linking it to task is we want to go one step further.

A task analysis is a common tool in human factor studies, and so our task analysis we can also use to conduct a use error analysis and a risk assessment, perhaps using a use-related risk analysis or URRA, and so this provides a method for us to try to directly link our design features to potential use errors and associate d risk.

So again, if we have this common task analysis where we have line by line identified our user interface features and on say a use-related risk analysis identified potential risks with each of those, we can try to link the two features.

Our development has come a long way. We started off with the visual card sorting visual taxonomy. We moved on to a spreadsheet that was built off of a common task analysis where we were able to line by line identify interaction points and labeling and include those definitions of categories, subcategories and descriptors. But through our testing we really see a research need for further development, testing and research related to making this a very user-friendly interactive software tool.
So our proposed research initiative is to develop a web-based user-friendly taxonomy for comparing user interface design features between the generic and the RLD and potentially now with the kind of advancements and availability of AI and machine learning just in the last couple of years, try to integrate some other tools to further understand and improve patient safety.

So this is our vision for further FDA supported research and development of the taxonomy itself. I want to emphasize this isn't something that’s actually been developed. It's really a visual graphical representation of where we think the research can go.

So let's say that we have a user interface that's a web-based design and through that we can enter all of our product information and we can build out an entire task analysis including tasks and even identifying subtasks on that task analysis. And then once the task analysis is complete, the program can walk through a series of steps asking about the on-device labeling, the specific characteristics of that labeling, asking how you interact with any software that's associated with it, what kinds of displays and controls you interact with and what kind of feedback you get from the device.

From there, it will continue to build out the analysis for a single device and give you a report directly linking the taxonomy to your task analysis, which could be saved and compared to that of another device and hopefully it would be able to highlight side by side where there's differences between the user interface of the two devices.

So how could this fit in the existing process? So we have mapped the process for the current draft guidance. Our research team, as you have already heard, likes to incorporate risk into it and so we think that if we did incorporate risk in the process, they're not required. You could have that URRA and on the step of the comparative task analysis directly compare those user interface design features to potential users and potential risks.

So how could AI and machine learning enhance this vision? There's some simple ways, perhaps, that we could have a system where AI can detect user interfaces, design differences on the interface of different devices through looking at images that are uploaded to the system.

If we were able to use the system as a common kind of database for collecting information on different devices from different drug sponsors, we could use the data that we gather to restructure the taxonomy as we learn more about the categorization and classification that are identified and patterns in the data may be related to device categories like whether it\'s diagnostic or therapeutic, the specific regulatory pathways, anatomical applications or context where and how the device is used.

And we could also perhaps learn and predict possible difficulty and hazards associated with design over time. We could gather information on if there are specific user interface design features that lead to potential risk, or if we could potentially link our user populations to specific difficulty with specific user interface design.

Of course, there are some big challenges here that would require a lot of human oversight. First of all, we'd have to have confidence that the source data would remain confidential. At a minimum, it is anonymized, but I think most likely the database of information gathered would need to only be accessible by the agency, and so that there's no confidentiality issue, the sponsors would be confident that their data would remain confidential.

The data volume - it would take time to gather a sufficient amount of data, and we'd particularly be concerned with making assumptions about rare user populations or instances where we have low frequency device use until we had enough data to kind of make those associations.

So we see great advantage to furthering research in this area of taxonomy development. We think there are obvious advantages to industry. The taxonomy guides innovation and ensures compliance and reliability with a process. It provides that repeatable methodology leading to standard procedures for human factors and submissions and creates a common language that designers, manufacturers, human factors experts and regulators can all use to communicate with one another.

I think that the advantages are even greater to regulators. It'll improve the quality and efficiency both of submissions and then of reviews with the consistent method for comparing these user interface characteristics. The taxonomy could act as a training tool for reviewers new to user interface design. And it could potentially even in the future link to adverse event reporting through other databases and provide an opportunity to integrate real-world evidence.

So with that, on behalf of my research team, Melissa Lemke, Mary Beth Privitera, Molly Story, and Molly Laird, I thank you for your time and I look forward to the discussion.

Thank you, Megan.

Moderator

So we can move to our last talk in this session. We can move to Russell Rackley. He is a Global Head of Clinical Pharmacology at Viatris and Russell is going to talk about the industry insight mainly about clarity and consistency for complex generics.

Russell Rackley (Viatris)

Thank you, Ahmed. I appreciate that. Yeah, I will be covering some collection of thoughts here that we put together regarding opportunities really for clarity and consistency for complex generics in keeping with the theme of this meeting. The views here are fairly broad with industry perspective and should not be interpreted as being part of Viatris's or its subsidiaries unless otherwise specified.

At the higher level here we summarized 6 different areas for challenges. Some of what you've already heard quite a bit about this morning, expectations around immunogenicity and purity characterization and also we just heard a great presentation on a comparative use human factor study design. Appreciate that.

Also, I will move on and really focus on three particular areas that I thought would - we've felt merited, you know, maybe some commentary in the areas of transdermal system, irritation, adhesion studies. Again, Priyanka gave us a challenge there to think about what to do with that in that respect, some challenges we see in patient bioequivalency studies and some comments around biostatistics, how they're employed.

To start with, I thought it'd be good for the irritation adhesion to go back a little bit into the history here of where this started actually. So this graph here is intended to show the test mean score versus a reference mean on the X axis, test mean on the Y axis. Now the FDA scores are constructed in a way so the lower scores are actually better performing in terms of irritation and adhesion.

Maybe that's intuitive for irritation. Maybe not so much for adhesion. That would be a possible thing to look at as well, but that's a different story.

But the original guidances were based on a margin set for non-inferiority, such that it was 25% of the test mean score. Basically, it scales as you go with increasing irritation means up to, let's say, zero to 2.5 in this example, and so 25% defined the upper limit for the confidence interval of the test mean.

This worked fairly well until you get to very low scoring which are good performing products actually. And in this case, the margin has become so narrow that it becomes overly sensitive. And in some cases you might even have a better test at the end of the scoring versus the reference, but still fail due to some variability aspects there.

The solutions - well, what we originally thought maybe was a good compromise there is to define a constant margin from zero to roughly one. That's just arbitrarily constructed and then allow scaling above that.

FDA's adopted implementation - I showed that here as an orange line for - this is irritation - was a constant margin over the entire range of the scores. So no more relative differences, proportions there for the upper margin, but was a constant margin 0.2 which actually solved a lot of the problems and challenges we had at the low end, you know, for both irritation and

adhesion.

It becomes more potentially problematic as you get into higher scores now there. Hopefully you don't see a lot of - now the adhesion was a little different. A little tighter margin. Their point of 0.15. Hopefully you don't see high scoring adhesions. In this case, that'd be poor performing, but irritation it does occur.

There are some products out there that are irritating. This is a stress test. 21-day cumulative irritation, repeat site administration or application. So this can be problematic as you get to occasionally higher scoring products where you could see some challenge there and showing or meeting that narrow, fairly narrow non-inferiority margin. So that would be an area maybe to think about how to compromise that even - can reconsider a kind of a mixed constant and scaled approach as you get to higher levels of irritation.

But there are other things we may want to think of in the realm of irritation, and I like the way Priyanka has kind of teed up some ideas there. So I appreciate that.

With respect to patient BE studies, these two things are kind of intertwined here. PK sampling in the patients and patient compliance. You do have issues in patient studies. They're done typically across multiple centers. Challenge to get recruitment. Challenge to get balance across sites typically and what we have seen is some degrees of variability across studies and how best to deal with that?
Sometimes they're isolated in nature as they could be due to patient compliance in the way that we see missing samples for patients and returns. Patients dropping out and sometimes very anomalous data, you know, with specific sites that I'll say.

So that becomes, you know, the challenges here, you already have high levels of quality oversight at these multi-center studies, but sometimes you get isolated cases of anomalous data. I'll say you know that maybe site specific. So how best to handle that? Needs to be, you know, factored in or addressed in some fashion.
And finally, some biostatistics points I thought we would probably make here in the area of complex injectables. Often you'll see requirements for partial AUC segmented across the profile, which we feel may be overly sensitive in some cases. Slight shifts in profile may not really make a difference or be clinically relevant, particularly if this is chronic administration with accumulation.
So maybe look at that and this - these are kinds of things that can be done, I would think fairly easily with simulations.
Highly variable drug products that are very highly variable. The challenge, even with a reference scale bioequivalence approach on that is the point estimate. The ratio requirement is - is required to be - the point estimates required to be constrained within 80 to 125 and sometimes with these I'll say very highly variable kinds of products you occasionally run into can be a by chance occurrence and these are already very typically fairly large studies, and I'm talking about intersubject CVs in products arbitrarily made some numbers up here 60 to 90 would consideration of a slightly relaxed estimate constraint 75 to 133 and even higher than 100. Let's say go a little bit wider. Not necessarily. This is a proposal, but this is to illustrate what kind of relaxation might be contemplated. And again, this could be done or evaluated through some simulation.

So those are some of the recommendations from biostatistics point of view. Maybe taking another look at addressing you know how we compare high irritating products with a non-inferiority margin and how to deal with very highly variable drug products in terms of you know

dealing with the point estimate constraint there.
So those were just some very high-level points to consider and I'll turn it back over to Ahmed and Brian now.

Moderator
Thank you, Russell, for the nice presentation.
So now we can move to the panel discussion and let me introduce first our FDA - yeah. Let me move first to introduce our FDA panelists.
So we have Robert Berendt, and Robert is Supervisory Chemist in DPQA V, OPQ of CDER. We have Andrew Clerman, Acting Lead Physician in DTPI, ORS of OGD. We have Lucy Fang, Deputy Division Director in DQMM of ORS of OGD. We have Bing Li, she is Expert Pharmacologist and Associate Director for Science in Office of Bioequivalence of OGD. We have Kimberly Witzmann and she is Deputy Director of OCC of OGD. And we have Robert Lionberger and he is Director of ORS of OGD.
Panel Discussion
So let me start with the first question here, and it is mainly about since we are talking about the future of the GDUFA research, what we are expecting in the coming five years. So let me talk about the novel delivery technologies like microneedle, like smart patches, or nose-to-brain delivery. They are all like novel technologies, so how can FDA proactively develop approaches for demonstrating bioequivalence of these novel technologies even before a reference product is reached to the market and even if the reference product just moved and just released? How can we develop bioequivalence approaches for these new products to help introduce generics to the market?

So let's start with Carla.

Carla Vozone (Catalent): Now we'll cover nose to brain as it is my area of expertise. I will maybe let the other members cover the others. So you know, as I indicated in the CNS therapies, they are a focus of attention for pulmonary and especially nasal routes. So you see 20% of the drugs in development are for CNS indication. So the nose to brain has a lot of potential because it avoids the blood-brain barrier. Of course, you know it's there to block the access of drugs to the brain. So the access through the nasal cavity is, of course, high potential for delivery of drugs like Parkinson drugs.

So but everything is quite in the early development stage. And from what I understand, the device design is going to be a critical element of innovation. So I would think that any research will need to pay attention to the devices that are being developed for this route as the device needs to propel the drugs to the nasal cavity, especially to the olfactory region of the nasal cavity to be able to be absorbed, right? So it's the positioning of the drug in the right place that is going to be really the driver of the efficacy of this type of drugs.

So I would say that device is important and then the same PK/PV models that we discussed for the pulmonary regional deposition, it's going to be applicable the same way for the nasal cavity, right. So the regional deposition in the nasal cavity is going to be critical. So any type of model that has been is being developed, I think there are synergies or knowledge that then can be leveraged for the nasal administration.

Moderator (FDA) Thank you, Carla.

So from FDA side, how do you think we can be prepared for development of generics of newly approved technologies? Bing?

Bing Li (FDA): I think I can address it from a very general way. I'm sitting here from the morning to this afternoon. I heard our expertise discussed explicitly the challenges of different dosage forms, different drug products, different tasks. Those challenges are the directions for the future research directions that we should go, I think. I don't have more to add on that point, but the two points that I wanted to add on is: OK, first, over the years we've already developed, we've already gained a good foundational understanding of the bioequivalence framework. For example, if we have a product that is a solution product versus a solid product, we know which way that we go, OK. And we have a product that is locally acting product versus systemic acting drug product, we pretty much know the framework of how we handle these drug products with added devices, you know, and etc.

So I think those fundamental frameworks will still exist and still be applicable for all products, whether it be the new novel drug product or the traditional drug product, that's number one. Number two is, OK, from the experiences that we gained from inhalation products, we may have a list of available tasks, OK. Say novel tasks that may be in different stages. It could be in the exploratory stage or it could be mature to tell the differences of drug products, OK.

I think what we could do is proactively take this list of part of these tasks, proactively working on identifying the very critical tasks that can tell the differences of the two products in terms of bioequivalence, OK. And then take that critical task, validate the test, make sure it's accurate, make sure it's validated and standardized. We talk about a lot of validation tests as part of the challenge, right, standardization of the test challenge, and then OK, furthermore thinking about, you know, after we get the data, how do we analyze the data, which is the, you know, statistical method applicable for those tasks and etcetera. I think those are the things that we can consider even without having an approved RLD product on the market, but we can still do that part of the work, get that part ready before we jump into, you know, having those products on the market. Thank you

Moderator (FDA). Thank you, Bing. So Brandon?

Brandon Wood (Teva) You know, just add a, you know, a couple thoughts there, and I think some of the new technologies are, you know, kind of putting a new spin on a long-standing technology. So maybe introducing tech to something, you know, a type of, you know, a needle that's been approved for a long time or introducing smart features to a patch. So I think one of the important considerations is remaining consistent with some of the long-standing approval requirements for the quote-unquote non-complex aspect of some of these new techniques.

So we can isolate the complexity to whatever is newly being introduced, right? So it's kind of scoping out or carving out the complex nature while being consistent in the approval requirements that we've historically seen on some of those novel techniques. You know, and then I just, I think it's also kind of a two-way road. I think it's important for the agency to just be transparent and open to new alternative approaches and kind of really lean on risk-benefit analysis and not such, you know, risk-averse approaches, but it's also incumbent on industry to make full use of any correspondence or meeting pathways as early as possible because, you know, kind of in line with what you were saying, Bing, is, you know, for some of these first-in-class things, it might be important for you to kind of learn along with us in our development so that you can develop review plans.

And I think even once, you know, RLDs are approved, we still identify research priorities because really it's not until we have an engagement with the agency and there's a difference in

thinking on a specific matter that we say, OK, you know, we need to develop more data here or, you know, we need to really elucidate this with the agency. So there's absolutely, you know, additional research topics identified even after RLDs have been approved because it's only when you reach that crossroads of a bit of a difference in opinion that OK, we really need some more information or data here.

Moderator (FDA) Thank you, Brandon. Markham?

Markham Luke (FDA): So on the topic of new technologies, I think it's really important for OGD not to be an island, that we maintain bridges and communication with the Office of New Drugs, which we do, and we continue to bridge with division directors there to see what the new products that are coming in are. It's also important for OGD staff to attend scientific meetings relevant to areas that they specialize in. And this is something that is, and maybe antithetical to budget cutting, but I think it's really important for us to have that ability to travel to meetings, to see what the latest technologies are and understand that.

We do know that not all the new technologies adopt; like, for example, the digital and some of the other stuff, they pop on the market for a short time and then they don't get established. But we are mindful and we do watch those technologies and see if they take and if they are going to have an impact on the drug ecosystem and whether we need to work on generic attributes for our product-specific guidances.

We have set in place, as you know, a system where every NDA that's approved, we've discussed this in public, that we triage the NDAs coming in and determine what's needed, what kind of research is needed for the product-specific guidance. So FDA OGD does have an established process together with OPQ, OPQ specifically, to address what kinds of research needs we have along with this kind of meeting that we're having today.

Moderator Thank you, Markham.
Moderator Yeah, thanks. So I wanted to switch gears to talk about a bit more about the charcoal block here, so sort of mains to numerous studies that's been added, and we've definitely gotten comments on the idea of what goes into the standard design for this and as well as thinking on, you know, the relevancy of other alternatives. So I'd want to put this to the industry. Maybe Brandon or Russ wanted to comment on given the focus for this, because again it is a PK. So, you know, there's particularly the costs associated with conducting these studies. What might be some research focus or studies that are, what will be a priority that we might want to focus on for this? Would it be, is there a greater, I guess, focus for, you know, trying to come up with making sure we have the standardized approach? Or is it the idea to, would there be more emphasis on looking for more alternatives to this because in terms of which might be of greater interest to the industry?

Russell Rackley (Viatris): I mean, I think this has pretty well already been discussed a little bit through today, you know, what the considerations might be for, you know, evaluating charcoal block. I guess my question back to you, agency, would be what are the expectations for justifying a particular charcoal? So it must be already some points there, you know, going through the minds of the agency as to we expect to see XYZ demonstrated. Is it going to be a specific product or product kind of evaluation, or is it, or could it be standardization? Is there in vitro testing that could be done? I think that was a comment that was made in one of the earlier presentations that could, you know, more or less validate your utility, you know, potentially for a charcoal, a specific kind of charcoal block.

Now, I don't know a lot about charcoal block, so I'm out of my field of expertise. But I'm wondering, is there more than one kind out there? Or is it all uniform? Is there variability there? So I don't even know. So those would be some things that I would have to start thinking about.

Brandon Wood (Teva) And the only thing I would add, you know, to that is maybe it's the regulatory professional in me, but you know, I think the paradigm of the charcoal block PK study is the current world that we live in, right. And while, you know, on paper, there's always opportunities for alternative approaches, from a regulatory perspective, that's usually starting to run uphill, right? So if it's prioritization, I'd recommend standardizing the charcoal block timings, administration, etcetera, so we'd have a clear read across there. While in the background, and then probably more call to action on industry, working on alternative approaches and soliciting advice from the agency along the way. But I think history would tell us that, you know, it's probably farther off than standardizing the charcoal block PK study.

Moderator Alright, thanks. So does anyone from FDA want to comment, or Rob or someone to talk about this?

Bing Li (FDA): I have a quick question. OK, we have two studies, one is charcoal, one is non-charcoal, right? Do we have data to say which one has a better linkage to the in vivo performance? I think I heard Andrew, you talk about the, was that you who talk about the PK study? The relationship of PK to the particle size? Maybe somebody else? Yeah, somebody else.
Yeah, I was just wondering, you know, whether there is such a comparison between the systemic PK versus the charcoal PK and their relationship to the performance?
Moderator (?) I mean, I would assume that certainly if there is, you know, a significant GI absorption and you're looking at or you're interested in the pulmonary dose, you know, that that might have a stronger linkage to say, like, realistic APSD. But I mean, obviously, if the charcoal block is not needed, then of course, then the regular PK study would be sufficient for that.

Rob Lionberger (FDA): Yeah. So I think one aspect of the charcoal block study that I think translates to other sort of novel study designs that we've seen is if you compare to what we do when we do, sort of tomorrow we're going to talk about solid oral products, and there, when we write a PSG and we recommend a PK study, essentially, every time the brand product and its labeling and the literature about it have described its pharmacokinetics relatively clearly, and they've done, you know, maybe they haven't done bioequivalent studies, but they've done a whole range of dose-ranging and drug interaction studies and food effects studies that look like PK studies, and you know, many of them show up in the label or in our, you know, or they publish them in the literature, that there's a range of information available about those. And so it's much clearer to write a design and a recommendation in the product-specific guidance that says, you know, we clear, you know, nothing, our intention in the product guide is to give a study that we know will work, right?

But when we move into more innovative areas, and I think this is part of the motivation for many of our even CRCG workshops, when we're doing something innovative, and one definition of innovative is the brand company didn't do this because they did clinical studies to get their product approved. And so you see this in immunogenicity, you see this in IVPT, and I would sort of put the charcoal block study in that pile of things with those where, because it's not a standard part of the pharmaceutical development for everyone, one, there's more uncertainty about that, and it's harder for us to write a guidance from the beginning that tells you very clearly what's going to work.

And I think that's just a recognition of that. You know, some of that can be addressed by research activities, but it also just as we've learned over time, it is more of an iterative process of going through the process of here's the best, here's what I think is the best approach now, I've done that, what did I learn from that? And you know, I think that's why we like the CRCG approach, right. We have the workshops where there can be that iterative feedback and improvement on some of these things.

I think also like the human factor study compared to abuse human factor studies is another thing that's not a study that a brand company would ever have done, but it's a, you know, it's necessary for the generic substitution. So that's just a framework of thinking about those type of studies differently and having different expectations for the guidances around them, but certainly it's very helpful to us to understand what places where there is uncertainty because some of them, some of them can be addressed through a research activity. You know, I'm not sure that we'd be able to come up with a general way to predict the right charcoal dose for everything, but maybe we have good PBBK models that'll tell you like, you know, we are doing some of that work internally to understand when to do the charcoal block study by saying what's the predicted absorption if you were to swallow this drug? So that's some comment on that in the framework for thinking about the research.

Lucy Fang (FDA): Yeah, I want to follow up with what Rob just said. I mean, first of all, I really want to thank the industry colleagues for sharing with us your suggestions on how to prioritize the research. So following what Rob said, that given all these gaps and the challenges, so there are definitely opportunities for modeling to inform the design of the charcoal block PK study. For example, the modeling can help you with the efficiency of the charcoal and also the modeling can help you decompose what's the fraction going to the GI absorption or the fraction goes to the pulmonary absorption, so through decomposition of spike modeling, you will be able to predict the PK like following the GI absorption, also the PK following the pulmonary absorption. So those modeling exercises will help you to design the charcoal block PK study so that that's kind of the opportunity we see in that map in there that is there. Thank you.

Brandon Wood (Teva): Yes, just one comment from the industry perspective. I think at times, you know, developing the model is dependent on data to feed into the model, right? So if you don't have that data, it can become a bit of a chicken and egg scenario, right? Because if I don't have data to inform the model, validate the model, inform the design, it's, you know, a little counterproductive. So I think industry would completely agree. I think one of the gaps that we have is the availability of data to feed into the model.

Lucy Fang (FDA): Certainly a commodity, that gap actually, I mean as Rob said, we're doing some internal research trying to really predict the PK following GI and pulmonary absorptions. And we actually had to use some data we can find from literature. So there's certainly some area we can work together.

Kimbertly Witzmann (FDA): Yeah. And just have one more comment. Hi, I think one thing that I really want to advocate for here again is also taking advantage of those pre-ANDA meetings to have these kind of communications from a regulatory standpoint. EMA has been recommending charcoal block PKs as part of their develop design development for a long time, but there aren't that many of those studies that have been published and are available in the data with very exacting specifications.

So when you're trying to build something for generalization, it's really hard because most of the data that at least the data that I've looked at that I've seen for PK charcoal block PK studies has

been in terms of different design opportunities or they were using it from a clinical perspective and they're publishing their data from their clinical study or something like that, so the applicability of all of those details doesn't necessarily translate to drug development and what we're trying to get at in these instances.

So having those conversations and being able to come to FDA and say this is what we've done, this is what we have seen so far, this is what, you know, the shortcomings that we had trying to do this so far. You know we use 10 grams of charcoal and everybody vomited in the first 12 minutes. You know that's an important thing for us to be aware of. And as a clinician, I, you know, I have a healthy respect for the fact that charcoal is not exactly the most palatable thing that we ask people to do even if we're paying them.

So, you know, being able to have those conversations look and see what's available, look and see what we've done to be able to help to guide those additional characterizations that for those studies that we may come up with, you know, I think it's going to be again, it's an iterative process. As Rob has said, it's not, we're not, it's not going to be a one and done. Oh, we have the perfect idea already in our heads. It's going to be informed by that information that we get when we communicate with industry. Thanks.

Moderator (FDA): So, so we do agree that we need to invest more about the design of charcoal studies. Yes. And I think it's not only from the clinical perspective, it's also from the physical, chemical perspective of that option of charcoal to specific molecules that of interest. So I believe some sort of mathematical modeling of that option isotherm that's happening to optimize the amount of charcoal and to, I would say, limit food effect and food interaction. Maybe this is direction to go and it was investigating research.

So just moving gear a little bit to the device perspective. So we have heard about the taxonomy interface approach that Megan shared with us. So I have a question about the like, what are the current research gaps that hinders the use of taxonomy-based approaches in user interface device design for generic device combination product and what are the research studies that are needed to understand how changes in the device design can affect the clinical performance and patient adherence from a user interface perspective?

So let's start with Megan.

Megan Conrad (University of Detroit Mercy): Yeah. So, well, first of all, we discussed the further development needed really to formalize kind of that process for identifying whether that's with a taxonomy or another method for identifying those interfaces. And we like the idea of a digital interface that's free and available to everyone so everyone has access and is encouraged to use it.

We know from having human factors practitioners test out the taxonomy and also presenting at conferences that this is something industry is very interested in. We've had requests to already use it even though we weren't even when we weren't done developing it yet. And people reaching out to out of conferences asking to test it. So we see that that is something that's really interesting to us to see the need for this, the structure and the repeatable process.

With an industry, I think it is difficult to at this point. I talked about ways to link or associate risk with user interface design features, but that's a place where further study will need to be done. There was a draft guidance in 2024 using URAs, though not specific to generics, but that's a process an FDA recognized process that could be incorporated with comparative use human

factor studies or even just at the comparative level the comparative use human factors draft guidance talks about identifying external critical design attributes and other design differences.

So maybe if we have a taxonomy that gives us a language, we can further look at future GDUFA studies that could, I guess I would encourage a future comparative use human factors research study, selecting more robust data. Maybe incorporating URAs or other forms of risk analysis and looking at not just kind of the framework that we already have for counting use errors and looking at use error rates, but also incorporating how close calls and difficulties affect patient risk. Or I should say, patient safety or inherent risk.

You mentioned adherence too, so adherence is a tough one to measure. If we're looking at studies of adherence, I think we have to take a step back and really, you know, it's almost measuring the immeasurable, so we have to take a step back and look at how we're defining adherence. If we're defining it with different components, maybe the not just if the patient takes the medication as prescribed, but you know the in different components, if the prescription is filled, they take the medication and then the understandability and on how to dose and how to administer the dose. The user interface seems to relate most specifically to that, that component of understanding how to administer the dosage.

So I guess to study that I would recommend looking at not just behaviors that lead to adherence, but we need to understand what behaviors and issues lead to lack of adherence and so doing contextual inquiry or research methods that really observe and interview people in the natural environment of device use and understand maybe why they perform tasks in a certain way and why adherence isn't, is or is not happening and then it would have to be really carefully crafted research questions like what are the reasons the medicine isn't dosed properly and what is the impact of design features on these behaviors?

So we'd have to be careful. It's hard to conduct true human factors studies and like a clinical study. Ethically, we want to be careful with that as well. But if we do contextual inquiry and use research methods, observing and asking questions, I think we can get to kind of the initial framework for what where we'd want to go with future research.

Moderator: Thank you, Megan. So far from FDA's perspective, the clinical performance. Andrew, what do you think about device perspective? How can the device design affect the clinical performance? What type of research is that we need to invest in it?

Andrew Clerman (FDA): So that's a good question. I mean in terms of the taxonomy, I think if we can kind of focus on validation and implementation of that, it'd be very helpful. And I think I think the device space is also kind of one of the areas that's ripe for use of machine learning in AI, because the things that can go wrong, the problems you're facing are pretty discrete. It's not like the exponential complexity of human biology. I mean people are going to use devices in certain ways.

You can probably somewhat quantify kind of what can go wrong and I think incorporating risk is something we already do inherently like as a clinician we when we see these devices, we think about what's the context of use, what can go wrong or think patients going to miss doses? Could they overdose? Could they underdose? And what would be the consequences of that?

So we're already kind of implementing that, but I think a more structured way to implement that would be very helpful. And then also have something that's more available to industry so that they can understand kind of what we're considering and provide a framework for how to think

about risk and present that risk analysis to us. And I think the URA is kind of a good starting point for that. But obviously within the generic space, we have to think about substitutability in addition to just the risk of the device itself.

Megan: Yeah, I think there could be a, sorry, I think there could be a development of a good process for a comparative URA that would then be used alongside of your comparative device and labeling assessment as well.

Moderator: Yeah. Let me move to Dr. Lionberger. What's your expectation from generic landscape about the device-based taxonomy?

Rob Lionberger (FDA): No, I think we're open to different approaches and thinking about how we make the reviews of the, the reviews and the development more efficient. So I think that is, you know whether this taxonomy is the thing I think that's not really something that you can comment on here. But I think the idea of saying can you put thinking about devices into a more structured framework would help the development and it might make it easier to see you know our our review.

You know Kim can probably talk more about this in terms of what the review look at when they look at, you know the trainings and the user guides that we give to our reviewers that do comparative analysis and what we expect them to look at. You know, as part of the interaction with that, because I think we want to be transparent about that. These are the things that we're looking for. Consider them in your design and that can make the whole process more efficient. But I think Kim probably has some good comments on that.

Kimberly Witzmann (FDA): Yeah, just briefly to add, I think when we go through those comparative analysis and again I want to focus those comparative analysis, the comparative tasks, the comparative labeling and the steps for use. We look at those very carefully when we have those, when those come in and as to compare to and again we're comparing to whatever that reference listed drug is for that product.

So what works for one and maybe perfect for one, may not necessarily even the same device. You can't take it necessarily and be able to utilize it for a different product in a different patient population or sometimes even the same population. If you have a different API, for example, that you're trying to use it for.

So I think that again it's that comparison back to whatever the reference is, because we do have to, you know, we have a mandate for substitutability and we also want to make sure that we maintain that therapeutic equivalence, which is the same clinical effect and safety profile as the RLD when used in accordance with the labeling.

And so as we go through those steps, that's constantly in our you know, we train our reviewers very carefully to consider that as they're going through is and it came out in one of the earlier sessions about, well, can't we just remove steps and be better? And it's a little tricky because we want products that are robust. We want products that are durable. We want products that are out there that are good, but at the same time we have this mandate to be the same.

And so sometimes balancing those two is a little bit tricky. But we do try to, you know, we do try to reinforce that as we're going through and looking at things. And I just want to put out a plug there. We have received URAs in generics. We do use them heavily. A lot of the, you know, as you're going through the steps for use, that's half and URA in in some aspect and many times

whether that risk benefit part is used as a justification within the body of the application, or if it comes in a nice table for us in the URA specifically, we're constantly looking for that information and if we don't have it, we send in, we send IRs to get that information.

So it's not as though we're not using that already, we're already utilizing that in our review processes. I think that the more that we can do to standardize things, to make it clear for people that this is what we're looking at, this is what meeting can be helpful and I think that you know, coming in the future, I think we'll have, you know, having continued conversations like this will help to firm up those recommendations in in a more transparent way. For that we can provide. Thanks.

Moderator: Alright, so one of the final questions here. So we did hear about the fact of necessarily getting out to novel devices and trying to be understand their complexity in, in interpreting it ahead of time. So with this, as we look for, you know, the challenges from say like novel excipients, the idea would be you know what, what, what, what specific excipients might be of interest that we might want to focus on. So I did want to start with Robert for this to see if he had any comments for that?

Robert Berendt (FDA): Thank you. So I you know, I want to take a little bit of a step back and kind of continue on what something Markham shared. Currently we have a process where once an NDA is approved for a new product that the agency gets started right away on understanding how we can develop guidance and any research that's needed to facilitate generic drugs coming in.

So I think that that's and that that's very much in line with everything I've been hearing today. There's been a large focus on PSG development and getting the new complex drug, you know, developed new complex generic and submitted to the agency. But what I think is also really important for us to think about and it comes to Brian's question about excipients is thinking about post market so I know. I know there's that first hurdle. That's super important like get, approval of your generic product.

But then once it's approved, I mean suppliers of excipients will change. Manufacturing processes will change sites. Sites will change all of these changes will occur, and I think that it's really helpful for us as an agency to be considering when we're doing PSG development and some of those initial characterization studies. What are some of the things that are critical understandings, not just for the generic to be initially submitted and approved for market, but what information do we need for that to be a product that will be successful for the for the long run to provide that benefit to, to the public, and I think we in our PSGs, a lot of the quality related aspects that we include in there as far as you know looking at morphology of API or you know various in vitro testing all of that is helpful, but I think that it's it in all of these discussions, although the focus is on getting it first, first in as an ANDA and then that initial submission and the product development. I think it's always helpful for us to keep in mind that long term approach that we do want you to be successful in producing a product that will be there to benefit the public for the long run.

Moderator: So. Alright, Carla, do you want to comment?

Carla Vozone (Catalent): Yeah, I'd love to. And really, you know, especially for pulmonary delivery the number of excipients that are available for the industry is very limited. So I would just build on what I presented and the fact that the spread ranges expanding that list a little bit

more, right, because you have more excipients that have been submitted. There's NDAs and they are in the market already.

So I would imagine that future generics will use those and I will highlight. Maybe you know there are excipients that are used for the stability of the API and there's also for the shell forming component, you know for to shape the particle that some of the particles I presented so I would say that amino acids are important. They are, you know, the LDL isoleucine. They are typically used also sugars for the for that stabilization of the API and the phospholipids that are normally they. They are shelf forming so they form the particles so those are the maybe the three excipients I don't know if that is even possible under the OGD but if there is research that could qualify to the industry alternatives within those categories.

I think it will be important to expand the access right so that the industry is not limited to the ones that are currently approved.

Moderator: Right. Are there any other industry comments, Russ, do you want to provide any?

Russell Rackley (Viatris): Nothing to add really. I mean, you know, it's all about, I think looking at the functionality of the excipient, what is the critical quality attribute? How does it affect misformulation sensitivity? Why so? It's a risk assessment.

Moderator: All right. Thank you. Alright, so since we've, you know due to time, certainly we appreciate the discussion here for this session. Lots of interesting ideas and certainly we'll be considering them for their research priorities. So with that, we can close this panel discussion and move to the closing remarks from Ahmed.

Closing Remarks from Ahmed Zidan
As we are concluding our first day of the workshop, first of all, I want to thank all participants. All like industry speakers and panelists. All FDA speaker and panelists and the brainstorming that we had today about the challenges to shape our research interest in the coming year.

So let me begin with like what we have done today. So we started with opening remarks from FDA leaders. Setting the stage for the importance of our work in advancing the generic drug development and then we went to our first session where we delved into assessment challenges with complex active ingredients, focusing mainly on peptides and oligonucleotides. And we have identified several critical areas for future research. For example, advancing the immunogenicity risk assessment methodologies for biopartisan peptides and the developing standardized approaches for characterizing impurities in these complex molecules and exploring novel analytical techniques to better understand the structure function relationship in peptides and the feedback from industry also emphasize the need for harmonized guidelines and collaborative efforts to address these challenges.

And then after lunch, we went to our second section. Where we focused mainly on the importance of methods standardization for complex generic like inhaled and nasal drug products and bioequivalence predictive methods and potential of in silico modeling. And we have identified some valuable insights for research priorities, for example, standardizing in vitro methods for inhalation and nasal drug products. And advancing bioequivalence predictive in vitro characterization technique to better correlate quality attributes with the in vivo performance and also enhancing the in silico modeling capabilities, particularly for orally inhaled products and how we need to develop integrated approaches that combine novel tools like microstructure technique into mechanistic PBPK modeling.

And our last session that we just finished, I believe we have identified some research opportunities regarding refining methodologies for establishing equivalence of transdermal delivery systems and orally inhaled drug products and exploring application of AI and machine learning in device taxonomy and comparative analysis and addressing an evolving regulatory landscape for complex products like combination drug product, combination product and investigating novel approaches for irritation and inhalation, as we discussed in the first talk.

So this outcome will significantly inform our GDUFA research priorities for the coming fiscal year. And we aim to align our research initiative with these identified needs to advance the science and generic drug development and assessment.

So thank you again for all of your contributions. And with this said, let me say have a good evening and thank you for your participation.