BIS-FDA-Fiscal Year 2022 Generic Drug Science and Research Initiatives Workshop
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>> Robert: Good morning, everyone! Welcome to our FY2022 generic drug science and research initiative public workshop. I'm Robert, the director of the research and Standards in the office of generic drugs and it's my pleasure to welcome all of you today. Thousands of you have registered for this workshop. Many will watch the asynchronous recordings that will be available after the event but I especially want to welcome all those who are here to participate live in this event. We have some special ways in which the live attendees will be able to participate and we look forward to full and thoughtful engagement with our workshop today. So first let me go over some of the logistics in our workshop. On the open page and on the web page you'll see the links to the workshop agenda and the full biography information. We have a wide range of fantastic speakers with huge and important backgrounds, perspectives on them, and I encourage you to look at the

biographical information to see all of the things they have accomplished and the experiences they have to bring to our comments for this workshop. Those are all available in great detail on the web page.

As I mentioned before, we have ways for live engagement in this workshop so we really appreciate those who are online live. So two things you can do to participate in this. One is, there's a Q & A box in the Zoom for you so as the presenters are presenting, you can type your questions for them. You can also type comments for them. We'll read all of the comments that come through the Q & A box. They'll all be included in the processing of all of the things we hear from this meeting so any comments you have, you can type them in there right away and they will go right into the system as well as looking for questions and our moderators will, if time allows, bring some of the questions to the panel discussions.

There's a few places in this workshop where we have the opportunity for attendees to ask questions directly and speak. So in those cases when we indicate that, please raise your hand to speak during the open microphone session and if time allows, we'll allow some live participation where people can participate in the discussion. Following this event, the transcripts are available on FDA's website as well as the archival recordings but as know, we know many of you are participating in the workshop from around the world so we will have, in addition to our live streaming on the center for complex generics YouTube channel, they will have the recordings available immediately at the end of each session.

So if miss a session and you want to catch up, go to the YouTube channel and you can watch whatever you missed during the day. Go to the FDA website for the long term archived version of this when it can be available forever. We want to maximize the ways that you can engage with us in this workshop. So why are we here today? So this part of our annual agreement to seek public input in our science and research programs that are supported by the generic drug program. This is the opportunity for stakeholders from industry and other groups to provide input into the process by which we try to maximize accessibility of generic products, try to make the development of the generic products, and outside of FDA, to help us make good decisions about where science and research investment

should go.

This changes over time as the industry and environment changes, the competitive environment changes, the public health environment changes and there's some scientific advances that may provide great opportunities for generic drug development. All of this is why we do it every year to try to hear what currently is on the agenda, what new and emerging topics we should be looking at. An example is the product specific guidance that FDA puts out is very important to generic development. Which guidances at which time? This is a very important question. Is there a new technology or new approach that might be appropriate for the inclusion of a specific guidance? Is there a specific product where the time line for development is really critical and you want FDA to really focus their scientific efforts on developing that particular guidance at this particular time. This is something we love to hear during the comment process at this meeting. And we have many and various ways to provide your input at this meeting. So certainly we have speakers who are presenters who represent diversity points and we work for the center of complex generics to get a wide thought and people in science to participate. These people make their formal presentations. There's a panel discussion where FDA will engage in discussion with our panelist and speakers as well as the comments you make through the chat to bring out any aspects of the discussion of presentations that you think are important for FDA to be considering as we develop our science and research programs. So you can write public comments through -- oh, there's an open public comment period where people could sign up for. There's the chat, of course, and the formal docket. So if you think of something during this and you or your organization want to make a formal public written comment to this, you can do so through the docket. The federal register notice for this meeting has instructions on how to make confidential comments to the docket as well.

And this meeting is a little bit different than the meetings we have had every other year because here, as we're moving into the renewal of the GDUFA agreements and the beginning of GDUFA3, we want to think about the next five years of the science program. So we have asked all of the panelist and speakers to take a slightly longer term perspective and think broadly about what areas FDA should be looking into that has the biggest impact on the generic industry for the next five years. We really look forward for the thoughts of our distinguish expert the and industry professionals with this

aspect of the program.

I want to go through the agenda a little bit and talk about what is so interesting about each section of our agenda. So we'll be kicking off after our keynote introductory remarks from Sally with an industry perspective panel. So this is driven primarily by our center for complex generics so I want to really recognize Anna and James, the co directors of the center for research and complex generics of reaching out to the generic industry in lots of different ways through different focus groups, different meetings and discussions to really draw out and at different levels in the industry as well. Not just the regulatory affairs but also the scientific staff and industry to really draw out in a broad way some of the challenges facing the industry in the development of generic products.

So we'll start off with some of the perspectives they have heard from these interactions but then we'll also have four different speakers from the generic industry, senior leaders who have generously given their time to participate in this event and they will also provide their individual perspectives on when they think the priorities of the next year should be. It's a great perspective. As FDA, it's our mission to provide access to the affordable and safety generic products and cannot be accomplished without the generic industry making choices to develop those products and bringing them through the process. So this perspective on what aspects of our science and research program will have the most impact on choices by the generic industry to develop products to enter into that to provide competition to invest in developing complex generics is a critical part of making the research effective. We really appreciate all of the distinguished leaders who have taken the time to provide these perspectives.

The initial talks in the first session will be recorded but all of the senior leaders will be back for a final session, for a live discussion with me about the next five years and we hope you'll come back for that and really hear that dynamic interaction between all of us as we consider what these challenges will be and I look forward to that immensely as the closing highlight of this workshop. So following that in the morning, we'll going to move into a discussion around model integrated bio equivalence approaches. If you think about the future as compared to the past, oftentimes for generic products, we were focused on do this bio equivalence study and everyone does the same bio equivalence study. In the future,

especially driven by much better models of drug pharmaceuticals, we can focus on the different products and differences they have. That becomes a very product specific discussion and requires input from models or other knowledge management systems and there's challenges of doing this efficiently. So we have great session on focusing on what we call a model master file or a way to separate the -- because you know, wait a second, FDA has looked at this and already approved the model. And I think this is a fantastic improvement in what whatever broad discussion on the science and research work we can do to develop this concept and make it work.

Another aspect of model based development is going to be over the next five years is increased importance of artificial intelligence and machine learning and modeling development. And I think actually using the perspective I have on this is, as we use models more, we will be using artificial intelligence and machine learning to speed the development of models for specific products. The scope of the generic program is so big you want to do it efficiently. So we look forward to innovations and creativity in this area. Also, helping to make generic product development more efficient. Then we'll move into the public comment period. In this session, we'll hear from our speakers who signed up but we'll also have a live open microphone for other public comments to be heard.

In the afternoon of today, we'll be focusing on excipient effects. As you know, so we want to focus on understanding the differences, developing the products, using those differences to develop efficient and effective generic products but also, as you will see from some of these sessions, developing some of the science around understanding these excipients that help address the issues on pharmaceutical development. The most current one and will be with us over the next five is our understanding on how to understand the excipients to understand the importance of nitro. This is not just limited to that but the issue related are also important for the development of complex generics and the role of the excipients in these products is of increased importance in the development of complex generics as well. We'll talk more about this in framing our discussions over the next five years.

In day two, we'll move to a discussion about the global nature of generic drug development. Currently, we have under way, an harmonization process for M13 for our immediately release bio equivalence. We have a new pilot program for

parallel scientific device on complex generics between FDA and EMA that is ongoing right now. The companies can participate today. But in session, we're looking to say, what are the opportunities and challenges around global harmonization aspects of generic drug development where we can achieve benefit from harmonization and the scientific challenges both in modeling and assimilation, excipients, complex generics that we want to invest our science and research efforts to move the issues around harmonization in the next five years. So this is a good way to look at what it looks like in five years and the areas we may focus our science and research activities on developing and having harmonization.

Next session, day two, we'll focus on complex generics. The challenge with complex generics is, we have developed in GDUFA1 and 2, that are more efficient, in vitro based approaches but there's a lot of challenges with implementing it. It's a novel and analytic model, how do I get it work? If it's a new technology, how do I work it through the ANDA review process? So when we focus on these science and research activities on making the development of new scientific approaches implementable in an efficient way. So we'll have a session to focus on that on day two.

Our final scientific session on day 2 is focused on drug device combination products. So many of you know that this is an area where there are many challenges for generic drug development and one of the most important ones we'll be facing over the next five years has to do with the user interface of the generic products. This is an important product development question but also public health question around allowable differences between brand and generic products. There's a balance in this. The science and research work that we do and support under this will balance it. If we get it right, we'll have a viable, competitive environment with the complex products with user interfaces that may have some differences, but also may provide to patients substitutable products they can use effectively but there's a lot of understanding we need to build up to do it right and there's a lot of fundamental public health challenges on the balance between similarity and competition in this area. So we look forward to a robust discussion around this in identifying signs and research challenges that we can use to address that.

As I mentioned before, our final session is a live panel discussion with our senior leaders from our first session as well as some other participants from FDA. And other groups,

you know, broad discussion around the next five years. I'll be leading this discuss live. I think it's a fascinating discussion and I hope you can participate and be here for that. So that concludes my introduction. For the next session of our meeting, it's my great pleasure to introduce the director of the office of generic drugs, Dr. Sally to give our keynote introduction to this workshop. So Sally?

>> Sally: Rob, I appreciate the warm introduction and looking at the agenda, it just looks wonderful! I'm just looking forward to it. Good morning, everyone! I would like to take a moment -- can you hear me okay now? There was a little bit of a delay, sorry. Okay. Rob, thank you! Thank you for the warm introduction. Well, good morning, everyone! I would like to take a moment to thank each one of you on behalf of FDA's office of generic drugs for joining us today for the FY22, generic drug and research initiative public workshop. As I'm sure many of you are aware, we have held this workshop annually since they made the amendment ins 2012. This is the corner stone of our group, the science and research program. The conversations that we have and your feedback from this workshop help to shape our science and research priorities for generic drugs. Also, I want to take a moment to ax knowledge this is our ten year anniversary, ten years of collaboration between the FDA and the generic drug industry. I look forward to the continued success.

The program creates enormous value by establishing increasingly efficient approaches that industry can use to develop generic drug products. This translates to great value for patients by providing them with an earlier access to high quality affordable generic products. In particular, it offers opportunities for targeted generational new evidence and new knowledge in the areas of high complexity and challenge. For example, we know that complex generic drug products are hard to develop with many facing unique scientific and regulatory challenges and this is why we have several enhanced efforts in place to ensure applicants have the latest information they need to meet FDA's standards for approval and ultimately improve patient access to these important treatments. Product specific guidances or GSGs are one tools that perspective applicants can use to focus their product development, prepare for the submissions and mitigate certain risks associated with generic drug product. This also helps FDA to expedite the assessment. In fiscal year 2021, the FDA showed 125 new and revised which 53 of them are complex products and over the life of the program, we are sure that nearly 2,000PSGs. In addition

to forming FDA guidances, our outcomes also allow FDA to clarify whether proposed by approaches presented to FDA in the product development meetings are likely to be suitable in preparing their submissions in a manner comparable with the most scientific regulatory expectations.

In fiscal year, 2021, there was 81 product development. The research outcomes also prepared FDA to access index references complex products which ultimately improved patient access that were proven to be unfeasible to develop even a few years ago. Through these efforts as well as the scientific workshops like this one, enhance the communications -- a few examples of the complex -- science and research include, first, long acting injectables. During FY2021, the science and research program continues to invest in developing new methods to have the bio equivalence of long injectables or products to help address barriers to perspective generic applicants demonstrates that proposed products are comparable to the preference products in which it becomes available at the site of extraction.

Also, in 2021, the initiated research in new areas that aid in developing generic drugs including IN carbohydrate products. These products have played a critical role in playing IND deficiency which affects around 5 million Americans and which disproportionally impacts women and children. The program is also investing heavily in research development, more efficient approaching to developing the generic inhalation products to establish clear, consistent, evidence based approaches to compare how differences between a reference product and generic drug device combination product impacts the patients. During this workshop, you will hear more about the combination products user interface design, and research that can help to assess and compare perspective generics with their reference products. For more information on this and other --

>> Hi, Sally. I don't know if you're aware but your PowerPoint slides are not advancing for everyone. Could use please just stop sharing your screen real quick and reshare your PowerPoint?

>> Sally: Okay, let me try again. Okay, do you see it? For more information on this, if you missed it, I encourage you to read the FY2021GDUFA science and research report published in March of 2022. This important work will continue as we close later this year and prepare for the implementation of three.

This once authorized by Congress, will include several enhancements to identify hurdles early and target research that has the development of PSGs and other important proposals for this program. And of course, the ultimate goal of this robust group science research program is to ensure that American patients have timely and affordable access to many modern drugs that are complex in nature and challenging to develop as generics. I hope it advanced to the next slide.

The availability of the complex generics from multi precedent sources diversifies drug product supply chains and reduces the risk of drug shortages facilitating reliable access to medical drugs. In February 22nd, 2022, FDA approved single use bios to treat dry eye. As part of the program in 2012, the FDA study conducting research to develop the recommendations for this product. In addition to forming this drug, the program has helped address complex issues under analytical measurements and statistical assessment. Today, we have supported 16 research products late into this. Similarly, on March 15th, 2022, FDA approved the first generic drug of die hydrate, inhalation aerosol for the treatment of asthma and COPD. This has two active ingredients would not have been possible without the scientific insights gained from numerous projects under this complex products over the last few years.

As you can see, the science and research has been essential to the development and approval of this complex generic products. This in turn will facilitate patient access to numerous, other complex generic drug products in the years ahead. GDUFA science and research ensures that FDA's thinking remains current with evolving knowledge with the most up to date, scientific and technology insights. As I conclude my remarks, I would like to thank all of you presenters and panelist for providing your scientific input and our attendees for their support of this important research. And also, I would like to thank the volunteers to make sure everything is working seamlessly even though we have some challenges right now and I'm sure we'll have more, but I know that the content, the discussion, and the presentation will be just excellent! I look forward to all of the exciting discussions and presentations we'll be seeing over the next two days, planning for the next five years of the generic drug and product and research program. Thank you for your attention.

>> I would like to thank the organizers for inviting me on behalf of the center of research and complex generics. In my presentation, I will give a background for the center of

research and complex generics, engage how the --

Our center was formed about a year and a half ago, between the University of Michigan and the University of Maryland. Myself and James, are co directors of the center and we have the manager for CRCG. You can see our e- mail and subscribe to the this at www.complex generics.ORG.

The mission of the center is to increase access to safe and effective generic drugs through enhanced infrastructure communication, education, research collaboration across industry, academia and the FDA. Thus, we have three major goals. The first one is communication. This is how we perform our out reach to the industry to learn about the and to present this to the FDA and publications. The second mission is education and we are conducting a number of workshops last year and have many plans for this year and hopefully with the COVID restrictions coming down, we'll have some hands on laboratory demonstration and in person workshops.

The third mission is research and we begin some pilot laboratory projects and we start an introduction with both industry and FDA on some research activities. Here's some metrics. Over the past years, we have engaged with 300 industry stakeholders, we conducted a survey with 281 survey responses and had over 50 industry meetings of industry. We have conducted 3 education workshops with nearly 6,000 registered participants. We begin several research products too on modeling for long acting injectables, R one on oral drug absorption and another one on reverse engineering of complex three products.

Here's the workshops we plan for this year. There is the first one in June on in vitro release testing and in veto, on the ophthalmic injectable, implantable, inserted products. We'll have another one in October on the model integrated bio equivalence of complex generic product development and then in November, on genre topical product development and in December, excipients formulation assessment of complex genre products. Please register so you can get the announcement of when it's open.

This shows how it interacts with the industry stakeholders. We usually have, small, medium, and large generic companies with trade organizations and CROs as well as other stakeholders as well as the agency. We established relationships and have periodic meetings with the industry for every three to six months and VUP dated meetings with the FDA. We use the

information we get through this interview. We summarize them in the presentation. We communicate our funding to the agency as well as we communicate broadly in publications of our findings.

Through this communication, we come up with several topics that are constantly brought up by multiple stakeholders. They would be separated into such categories as communication, nitrosamines, clinical studies, and complex generics, alternatives.

Communication between the agency and the company often come up in our interviews and hopefully many of those items will be addressed in guide three. There's still remaining challenges with change in product specific guidances and clarity of the expectations that the FDA has with complex products on how the testing should be conducted, which leads to delay. It is especially difficult for the companies that have developed the first in class generic products when the past pathway is not clearly defined. Many times complex generic approvals take more than two cycles of the review. Not all of the aspects and questions are brought up by the agency during the first review and some of the questions are answered by the agency too close to the goal date and might lead to subsequent CRL.

There's all of this ongoing research and developing an understanding around the complex product. Which means that the time that the company holds, the new information is generated by the agency and so collaborative research, this University and it really needs to be communicated to the industry so they can adjust how they perform some of their analysis.

In addition, there really is a very strong need for PSG to come out of three to five years before the complex product might expire. Often the company begins working on the product way before the pattern expiration and there's some products that come up such as for orphan indication, like, pediatric, RNA based therapeutics that do require additional guidances. For some products, also, analytical characterization is described in the PSG very superficially which makes it difficult to establish the methodologies that are expected by the agency.

This year we see a very big impact of COVID on the generic industry. In general, there's very big challenges in the supply chain in the raw material API and significant delays in enrollment across the board but specifically in the respiratory products. There's a lot of shortages of the supplies across

the board but especially for injectable products. Glass vile, pre- filled syringes, sterile manufacturing supplies, excipients, everything was constrained. In addition, there are labor shortages and finding the talent is very difficult. Everyone sees significant inflation and there's a large increase in the pricing and shipping cost with various components that really delays a lot of approval and affects generic industry.

Clearly there is a slowing down of the ANDA filings due to facilities shut down, development delay and also due to inspection related delays. Nitrosamines is a major issue that is major issue. There's a reluctance behind investigating them which puts the burden on the generic manufacturers. This impacts a large number of approved products. There are technical challenges such as the low limits required very sensitive methods which is sometimes impossible to establish. Complex nitrosamines require a synthesis of reference standards that are also limited, and no toxicology data available for simple and complex nitrosamines.

There are some lack of clarity in the guidance on searching the limits. Both simple and complex nitrosamines are treated the same by the guidance, despite the differences in molecular weight and lifetime exposure is used to calculate nitrosamines levels that are sometimes only used for one week of treatment like antibiotics. There's a lot of potential for research under this. Standards and shareable reference standards control of nitrates in common use of raw materials and tablets. Understanding the solid state reaction and how the formulation impacts the reaction rates, use of antioxidants to reduce the nitrosamines, but then the buy equivalence Z -- by the agency to better defined the limit and the use of the method to prepare toxicity.

Clinical studies that come up in our discussion. The sample size especially for the inhalation product is very large and sometimes the cost of such input exceeds the cost of the development of the RLD. There's challenges in finding participants and drop outs for long duration studies. There's a very large in house that will impact development of drugs approved for orphan indications or pediatric patients that are stable currently on RLD and the number of patients is very small. There's a very strong need for harmonization of clinical study designs between U.S. and Europe and also they need to be able to use the RLDs from different geographies for the analytical comparability assessment. There is a very large desire in finding alternative approaches to bio equivalence

studies, especially for long acting injectables and inhalation products and can this critical trial be reduced by additional clinical characterization. Some research in this area would be very help. Drug device combination comes up very frequently in our discussions.

Devices are heavily predicted by patterns as well as trademarks which make very difficult to make a substitutable device taken together with high expectations that the agency has for the device similarity, making it very difficult to approve more of this complex products. There are also no available guidance on how to properly calculate the non inferior march to employ in the human studies. These studies have a lot of variables. There are several requirements on characterizing the variability of the plastics and yet, there are only one or two plastics available. In addition, the recent ruling of genesis medical technology versus FDA begins to impact other drug products that are employed drug device combination such as eye droppers.

As I mentioned previously, the development of alternative approaches to end point studies is very important. There's a significant need for these alternatives, especially in inhalation and long acting injectable products which are all over a billion dollar products with multiple companies working in this area. Yet, there is not enough clarity on what it will take to implement the alternative approach and when is the extent of the validation of such alternative approach required. There is significant ongoing research sponsored by GFUDA for inhalation of ophthalmic and other areas but yet, there's no regulatory presence on the translation of such science and INTER regulatory approval. The agencies very motivated in engaging in modeling approaches, however, there's many limited number of use case studies published and publication of such studies could increase the adaptation of modeling into the practice by the generic industry.

Last but not least is analytical characterization of complex generics. There are still significant challenges the companies experience when they file complex products such as long acting injectables, or ophthalmic products and they go for multiple review cycles and yet, there's still deficiencies found. There is some sort of lack of clarity about the expectations around extension analytical characterization of these products and there is also a strong need for better control and prescribed methodologies, especially as they prepare for the solution studies and particle precise

characterization and there are also some high expectation on the validation of these methods and many times, these methods are very difficult to validate on this. In addition, multiple companies bring up peptides and assessment of the sameness of peptides by analytical methodology as well as assessment in immuno general necessity. These items still remain very important for the generic industry additional research should be required as well as the publications of their findings.

In summary, we believe that CRCG has been effective in identifying concerns, challenges and potential areas of research to facilitate generic approval products. We truly appreciate our collaboration with the agency and the relationships we built with generic industries stakeholders that increase both our understanding of the critical factors, that the impact generic drugs and our ability to bring up these issues with the agency.

We hoe that GDUFA will come up with additional approaches for inhalation and long injectable studies. There's still a strong need in collaboration efforts aren't nitrosamines with respect to analytical characterization, toxicology and recipient control. There's still a need for publications around the characterization of specific complex products that are based on the GDUFA research and development of standards methodologies that could be used. Publications on use case studies for more than approval for complex generic products will stir up the use of the generic industry. In addition, we have to look forward to the products that will get a pattern over the next five years and develop PSGs proactively for products especially in the orphan indication as well as RNA-based therapeutics.

With that, I would like to talk about the acknowledgments of FDA. Multiple generic companies and trade organizations that we interviewed, Sam who is our grant manager, David and Lisa at AAM. Jim -- and two students in my lab. Thank you!

>> Bob: Hi, my name is Bob and I'm the senior VP global quality management. It's my pleasure to provide an industry perspective on JERic products and development challenges and research priorities as part of this public workshop. So I think a good place to start is looking at overall enhanced communications workshop the, educational tools for the development of complex generic drug products and also, alternative bioequivalence approaches that FDA and industry may consider for complex and other products. From a regulatory

approval perspective, industries often request clear, specific expectations in FDA during the this could really help for the timely approval and also, help the FD manage the workload of these complex products to get them out and available and accessible to the U.S. patients. Some examples and we'll touch upon some of these later on in other slides.

This is a request for FDA to present detailed case studies clearly showing generic drug industry the expectations of FDA and this will help reduce cycles and increase cycle approvals. And then we'll see a couple of examples of case studies we want to bring up as potential areas where there could be communication, additional research done to be able to help industry and the patients. We also request FDA to share current thinking on the validation of population PK or PBPK model when these modeling approaches are used to demonstrate bioequivalence and I'll talk more about this in a future slide. And also look at reimagining post CR meeting requests should not just be limited to clarifications questions. So providing the opportunity to ask targeted questions and for FDA to also ask questions so there could be a dialogue, again, to be able to improve the communications when it comes to expectations but also, at the end of the day, move along the approval process of these critical medications.

So specifically, let's look at immunogenicity testing for peptide drugs. FDA has been presenting information from a scientific perspective but there's a lack of clarity on the regulatory pathways and how to go about using those during the development and during the life cycle of these products. So there's some gaps as we see them. One, asking FDA to present detailed case studies showing the generic drug industry the expectations represented to innate and adaptive immunity testing which will help reduce review cycles as I mentioned before and have clarity around those expectations. At the early stages of product development, asking targeted questions related to this type of testing may not be feasible in a pre-ANDA meeting. In many cases, industry in the case that we have been hearing is learning more from consultants than FDA because those consultants are working in these areas on a daily basis. So we're really asking, FDA to consider other types of meetings or avenues to have that enhanced communication so that applicants can pose questions, and industry is asking to have a question with the FDA to get answers to questions about these types of studies and testing, specifically from peptide drugs. Inability to do this, will delay product development and product approval.

As I mentioned before, population pharmacokinetic or oral PBPK modeling when tests fail, only when the conclusion of outliers is challenging areas. Failure of these studies due to statistical outliers is a common phenomenon, exclusion of these outliers is not accepted by FDA. Therefore, studies are repeated with increased sample sizes, increased costs and delaying the approval of many critical medications. We see some regulatory gaps here and ask that FDA share current thinking on using these models, PK and PBPK models to demonstrate bioequivalence and not repeating the studies when they fail only due to the inclusion of statistical outliers. So recruitment of similar ratio of male and female studies is not always possible in these studies. That's currently a challenge that we're trying to over come in the industry. So we're looking at can populations PK or PBPK modeling be used to justify recruit of subjects from a single gender or recruitment when it's not possible or have a conclusion about the case studies or other FDA variances. And look, if there's a way with more global harmonization, to repurpose the data submitted in other jurisdictions. For example, generics versus an EU RLD for submission of FDA. This will give us a chance for significant time and cost savings using these types of models and a faster pathway for regulatory approval which is beneficial to industry, FDA and ultimately the patients.

Another area I think that there's an opportunity for additional research in addition to communication is the use of in silico.

Through published papers, FDA is providing scientific paper about in silico modeling approaches to evaluate lung deposition for inhalation products using, for example, computational fluid dynamics, CFD. We see some gaps, some regulatory gaps that would be beneficial to fill with additional research and additional communications and dialogue between industry and FDA. So FDA does need to provide clear expectations about the validation around CFD. And again, I think it's helpful to see detailed case studies on pivotal CFD data that is needed for approval. Regulatory flexibility in the validation approach for CFD when minimal literature data is available. And I think this type of approach is also then applicable to use and consideration of other alternative bioequivalence approaches which again, are going to be used more and more as we're developing additional complex generic products.

So another area long acting injectables. FDA recommends bioequivalence studies due to safety concerns and there's very

few LAI generics approved. During pre- ANDA meetings, they submit typically 1- 2 pilot BE study in healthy subjects. So the industry is looking to see, is there a way for FDA to be more flexible by leveraging safety data and healthy subjects from multiple studies and sponsors for the same drug product and be able to revise the draft, specific guidances to be able to put in those considerations. So in this case, single dose BE studies in healthy subjects instead of multiple dose studies in BE patients. Significant time and cost savings, faster pathways to regulatory approval and a positive impact to the public health yielding alternative and affordable generic drug therapies for the patients is the goal for industry and FDA. This is an area where additional research and additional dialogue with FDA especially looking at case studies would be helpful.

One other area in vitro permeation testing. This is very difficult. So the regulatory burden is increasing, has increased for these types of products. Requirement for skin donors from multiple skin banks is not always feasible so those are some of the regulatory challenges that we see. Again, there's the possibility of additional conversations, dialogue, and research requesting FDA to publish product specific guidances and then incorporate some of the common things they're seeing as deficiencies or issues related to these IVPT studies.

Again, detailed case studies would also be helpful for industry to have these conversations and lay out what the expectations are for FDA. Deficiencies related to these study KS be shared during pre- ANDA meetings and mentioned on the website and worked into the guidances if the issues are from a product specific nature. So we really wish to have further dialogue with FDA to share these concerns and that's an area where we can have a workshop and other dialogue.

There's a couple other areas as I wrap up that I want to propose. Maybe not from a research perspective but definitely from a development and life cycle challenge perspective. So one is impurities and APIs and drug products. I think this has been pretty well publicized there's a lot of information from FDA in terms of nitrosamines impurities but there's further guidance needed from FDA. How do we deal with this as the life cycle with post approval challenges. We have seen an up tick in more communications and expectations around nitrosamines like impurities related to specific APIs and in some cases, going back to the drawing board when it comes to a product that

has been approved from a development perspective. It leads to challenges, especially for something very complex. And then how do we use this approach for other products with other impurity concerns? The Azido. We see challenges here. How to deal with the impurities and also, what are is the next set of impurities that FDA is thinking about? What's the process that FDA is using to identify this next set of impurities that may be something we have to consider as industry or is there an opportunity for us to also discuss about impurities that we think might be something that needs to be addressed?

And I think this lack of clarity and communication with FDA impacts product development and really provides challenges from a post approval life cycle management perspective. So we're looking at could we have something like a biannual collaborative workshop in dealing with these impurity or the next set of impurities that could be a challenge for the industry in total?

And then the last issue I wanted to bring up is, early communication when it comes to data integrity issues especially around clinical research organizations. So the generic drug industry is striving to deal with CROs that don't have quality or compliance issues. As most people know, recently regulators identified data integrity issues and a few CROs that impacted a large number of ANDAs with a therapeutic rating and many of the approval of these. I think the gap is that early communication with industry about potential data integrity issues with the CROs so that the industry may pivot to assure study, data reliability is very important. If studies have already been provided to FDA, then we need to go back and start thinking about what needs to be done during the life cycle or soon after approval or during the approval process to be able to manage what studies may be repeated, what needs to be reanalyzed. And in waiting for the FDA investigation to complete is too late. We will talk about the drug shortages and the repeat of BE studies which is very expensive and an enormous public health burden because patients may not have access to the critical and in some cases, already approved affordable medications. It's incumbent on us to see this, and as soon as FDA sees it, to provide the clarity to the industry so the industry can react in a timely manner and show the product out there on the market that's been approved is bio equivalent and will not cause any safety or quality concerns to the patients who are desperately needing and using these products.

So again, I want to thank the FDA and the organizers for

inviting me to provide some perspectives and I hope that you enjoy the rest of the two days of this workshop. And then we have a chance for further dialogue. Thank you very much!

>> Good morning! I'm the senior vice president for Apotex. Thank you for the opportunity for presenting on behalf Apotex. As you look back, under GDUFA1 and 2 is very focused on making sure that we look at complex generics and create the pathways in a way that the research is focused on those products to create the pathway and I do believe to a greater extent, we're seeing it in the upcoming slide it has been accomplished. As I said, a lot of the work that was done funded by the GDUFA research has created a lot of approval such as suspensions, long acting injectables and a wide range of topical products as was put in the report.

As we have seen in the previous slide, the success you have seen on the various approvals. The next five years is about building on that success. So we believe that the areas would be the area around complex active ingredients, formulation and dosage forms, complex relative delivery, complex drug device -- and then also, more importantly, to make sure that we are able to maintain the continuity of supply and have the responses to some of the challenges that the industry is facing right now, one of them being the nitrosamines and you'll hear a lot about that in other sessions that are being held in the next two days where you have speakers speak about the challenge and what we can do about it. Next slide, please.

What I'm going to now do is for each of the research products we have identified, I want to talk about what it is we face today as a company and some of these options that are available out there to address these issues. I will start off by talking about complex API and formulation or dosage forms and talk about peptides. So as you all know, there's several assay platforms available for in vitro immunogenicity. This has not been clear defined. This is an evolving area and the current practices and tools are used in the scientific perception of the lab. We can consider establishing predictive animal models to evaluate the immunogenicity risk and the assessment.

Next slide, please. We have to look at the studies we have to do for the oral or inhaled products or other complex dosage forms. These are research intensive and the inclusion and exclusion criteria makes patient recruitment very challenging

with the typical studies that are going to last for about two years. It's about time that the agency should consider implementing in vitro methods to get the PK and certain other methods as alternatives for inhaled products.

Now, the approach will enable faster submission and approval of complex drug products. Now, when it comes to the complex drug device combination products, there's newer products being approved with the drugs that are associated with the mobile application. It's a drug device combination with the mobile application. So right now, as we speak today, there's a lack of guidance for drug development with the mobile app included as part of the drug product. Now, we are hoping that as part of the research, there could be the assay, the assessment for the need of drug developmenters to include these mobile drug applications and also, if it is needed, then agency will consider developing a guidance for the development of drug device combination that includes mobile applications. The other topic that I want to kind of impress upon the agency is on the complex drug device combinations like the transdermal, that there's method to enhance the adhesion, irritation and sensitive and possible alternatives. This is not suitable for the topical device components. So we're urging the agency to consider assessing potential in vitro methodology to serve as a predictive model for this, and as a possible alternative for the current in vivo studies. In addition, we urge the agency to evaluate the IID guidance with regard to the transdermal, topical device components such as backing film, linear membranes for the relevance of the IID listing.

Another area of listing for Apotex is PBPK modeling and the simulation for demonstration of bioequivalence. Time to develop the mechanic NISic models to predict in vivo. And this requires unrealest number of subjects to achieve the number of studies. This can be avoided if the agency can work on this, combined with appropriate statistical assessments for developing ultimate study design for complex products. Now, as we have developed the PBPK modeling, combined with the in veto test, that can be for the next. When we make post approval -- when we make non proportionally formulated lower strains. In goes to be used by the studies and will be very valuable in case of locally acting drugs in the GIT. Now, one of the ideas that have been floated in the past is, using an approach for bioequivalence study. Now, this has been effectively used by other regulatories like Canada. FDA's consideration would go a long way in that direction as well if we have a modeling that can demonstrate how the study conducted on a foreign reference

can be extrapolated to the U.S. reference.

We do believe that there is more work that can be done as for the tools and methodologies for the therapeutic BE concerns. We do acknowledge and thank the agency for considering one of its priorities to look at study interruption and protocol deviations as unexpected event, however, could also be expanded to include alternative approaches to handling the aberrant data. Observed outlier data cannot be excluded from the documented clinical or bio analytical cause which leads to the unnecessary repetition of BE studies. What we're hoping is that they can develop alternative BE approaches to account for unexpected EENTDs. Alternate approach the acceptable to FDA to interpret the data via statistics or PK modeling or AI to predict whether the observed data is biologically plausible would be helpful to limit the repeating studies unnecessarily. Next slide, please.

In summary, I would like to conclude by saying GDUFA research has been instrumental in supporting complex drug development for the industry. GDUFA research has led to several first generic approval for complex products over the last 5 to 7 years. We're looking for research in the next 5 years to be focused on creating a basis to use in vitro models in view of the clinical studies. Thank you again, for the opportunity of presenting to you what we're looking forward in the next five years.

>> Good evening. This presents a significant challenge in -- there are opportunities for research needed to better understand and acceptance of the science necessarily to bring complex generics to the market expeditiously. This presentation highlights challenges in the development of various types of complex generic products as well as recommendations for resolution. Impurities in generic peptides which is referring to the recumbent RLD. From this analysis, new impurities or impurities also present in the reference product, but at a higher concentration are handled on a case by case basis using the totality of evidence approach including in veto studies to evaluating the immunogenicity risk but there's many more guidance available for in vitro immunogenicity studies design expectations and this specific details are often communicated in complete response letters. Our recommendation is, if FDA could develop multiple, publicly available validated method the for innate immune assays and DC- T cell assays. Increased specificity for study design considerations would

enable sponsors to conduct the studies in line with FDA's expectations.

With regards to iron colloids. Comprehensive side by side characterization studies need to be performed on the drug product, the iron colloids, and difference between the test and references investigated and justified. There are however, no publicly available analytical methods for in vitro characterization, none that has been established by FDA. So deficiencies in CROs often relate to the way in which the products are characterized and insufficiency of characterization. Only during the review procedure does FDA request industry to follow specific methodology. The requirements evidence in various ones are continually changing and the in vitro characters that impact the in vitro performances are debatable. So our recommendation is that further research is done to develop appropriate methodologies with sufficient detail, sufficient level of detail for in vitro characterization and to develop guidance to communicate FDA study design preferences to specific to iron colloids that are clinically relevant.

For long acting injectables, FDA has indicated an interest in seeing modeling and analysis plans in terms of model based approaches for bioequivalence assessment if proposed as part of pre- ANDA submissions prior to execution. However, it has been highlighted that information requests are common for these types of pre- ANDA meetings and this takes away time from the assessment clock. Modeling integrated evidence can have a meaningful impact on reducing the study duration but the specific expectations are unknown.

So we recommend that you know, it would be beneficial to both industry and FDA if there was a mutual understanding of the information to be submitted in pre- ANDA meetings to make the most of the meetings and to set a strong foundation for data to be generated in support of an ANDA. So it would be helpful if guidance is developed that is specific to model integrated evidence with suggested approaches, designs and templates for submitting the information in an ANDA.

For drug- device combinations, there's no available guidance that represents FDA's thinking on comparative use, human factor studies, or how to properly calculate a non inferiority margin to employ in these studies. So FDA's current expectations for comparative use human factor studies needs to be publicly communicated. So we recommend that, regulatory science and research regarding the acceptable study

designs and NA margins that can be employed in these comparative human factor studies and this could include workshops, training and focus groups that would be beneficial to both FDA and industry. Research in this area could facilitate a common ground whereby other differences between test and RLD could be effectively, by the 505 gene pathway. Under the amendment to the Montreal protocol production and consumption of HFCs will be cut by more than 80% over the next 30 years. But there's still no clear guidance from FDA as to what is needed for generic drugs in the event it already switches to an greener propellant.

If required, what studies are necessary? Would the in vivo equivalence be sufficient to support the switch? Taken for respiratory drugs, are there opportunities for utilizing waivers?

There could be reduced inVOE toe data requirements for the establishment of the improved modeling but there's no guidance for CE waivers. So the recommendation is to develop general expectations for CE waivers, product and data requirements should be developed and you know, to provide adequate in silico modeling parameters needed to be outlined. Minimum requirements concerning alternative invitro methods, which would be with this.

With regards to transdermal systems, they often make changes in the type, grade, et cetera, while maintaining the same acceptance criteria. However, any change to an NDA is considered major, thus, potentially impacting all stages of life cycle management so we would like to see acceptable limits developed for changes in these and the data requirements to support the change. Another challenge is with changes in drug release specific specifications, these may require repeat PK studies, however, for a large number of products, IVPT is a tool to establish the equivalence so can it be used to release any changes in the IVPT? So what we recommend is the development of a mechanism to compare or correlate IVPT or in vitro drug release.

For semisolids, this makes it difficult for RLD selection for IVPT studies so the suggestion would be to establish the criteria for the RLD lot and guidance providing on how to address the observed variability in the final study outcome. Another challenge is the lack of procedures for addressing the ap rant, non robust data points for the IVPT studies so it would be beneficial to establish a methodology to address these

aberrant data points during these IVPT studies. Now, preservatives have a tendency to stick to the apply indicator. It is difficult to match it with the test product against it for Q1/Q2 so our recommendation is utilizing the preservative efficacy studies to support the Q1, Q2. Other general challenges are for instance, a lack of global harmonization. This makes it difficult to develop a product for the global market. Product specific guidance, there's a lack of product specific guidances for certain drug products and often the PSGs are unclear. So further refinement of the PSGs such as there's clear understanding regarding FDA's requirements for approval would be beneficial.

GDUFA promises to resolve these issues but we do have work to do. The lack of guidance for various complex makes it difficult for industry. So establishing SUPAC guidance for all established complex dosage forms should be worked on and made a priority. This will not only assist the industry but will also reduce the number of requests through FDA for guidance. So in conclusion, so much has been done, some challenges remain. There are opportunities for further studies to removal or alleviate these challenges. Industry looks forward to further discussion and to GDUFA III implementation. I would like to acknowledge my colleagues at Teva. Brandon, Alan, as well as the research and development team. Thank you for your time.

>> Good morning, good afternoon, everyone! Hi, I'm with (inaudible) pharmaceuticals. Today, I'm going to present on the advancing developments of complex generics to improve patient access to medicines. I would like to thank the FDA for the kind invitation to present in this exciting kick off session, the next five years of the generic product science and research program.

Complex GX, represents an untapped savings opportunity for the U.S. health care system, including patients, Medicare, medicaid, and commercial payers. Despite recent efforts to promote the approval of complex GX, these products are still slow to be approved and more needs to be done to advance and enhance access of these critical medicines for patients. Complex products are medical products where considering the pathways or possible alternatives.

These products are in general, harder to develop with traditional bioequivalence methods and therefore, fewer exist resulting in less market competition for these products. This

is where we as an industry can get more involved and potentially steer the conversation to a better inform FDA thinking around product development and innovation for complex products. In the next five years, a combined total of approximately 90 billion dollars in U.S. PhRMA sales are at risk of patent expiration. With approximately 14 billion from the injectable segment. This has 25 percent of the total number of LOE opportunities compared to ophthalmic or nasal, each at less than 5 percent. If we look a the injectable segment, there's multiple complex types of genics such as long acting release like lipsome products, suspensions, all with a large part of the LOE value being derive from peptides. To put in perspective, there's 13 approved ones from 18928 to 2021, mainly -- 80 compounds are currently in phase two and three and 130 clinical trials ongoing. And for peptides, greater than 80 percent were approved being for peptides during 2016 to 2021 and currently 170 clinical trials with peptides are ongoing.

Each of these subgroups have their on complexities and we'll go over the challenges and opportunities for advancing generics in these categories and also my colleague, will dig a bit deeper into the nucleotides and -- products in session six.

Generally, more complex dose delivery doses have on average, fewer competitors with higher barrier entry due to the complex requirements. This has multiple challenges stemming from material complexities such as API excipients, formulation complexity, manufacturing process complexity, analytical methods and in vitro BE complexity. For example, where multiple orthogonal methods are needed and to demonstrate sameness and challenges of sample due to formulation, matrix interferences.

Access and availability to the desired CROs, equipment, and resources skilled in the art of developing complex generics. Regulatory complexity and bio complexity, for example, demonstrating bioequivalence due to high, inter or intrasubject variability when such studied are needed and lastly -- be advancing in further advances development of GX products for the US market. Now, let us take a look at trends towards complex GX.

So one of the first trends here is, we're delivering more value to patients by addressing unmet needs and enabling market generation. Some companies are moving focus to complex generic

products. So the focus on this is critical because these drug products provide important therapies to patients and also are becoming increasingly significant to the economic health of the generic drug industry. For example, in an article published in February of 2021, the expected drug savings for GX, assuming price discounts from 30 to 44% and generic market share, the expected savings is approximately 25 percent of the annual grand sales. Now, I would like to go briefly in some areas of opportunity for additional research considerations that can help advance the development of complex generics.

Regarding synthetic peptides. References to R DNA, RLD, FDA published guidance in May of 2021. Now, they provide scientific evidence regarding what the number 0.5% and 0.1% were based upon. This presents an opportunity for further guidance and research for this area. For example, can the regulatory impurity limits be based on solid scientific justifications that could potentially allow for higher limit, level of limits without compromise to the safety and efficacy of specific peptide drug products. Further active research in this area is encouraged.

Further opportunities exist for peptides regarding immunogenicity. Can they provide a clear flowchart that and further detail in the insights and out comes in this topic area. Next, we would like to briefly highlight opportunities for lipsome products. Although two products have been approved, some further opportunities will include establishing guidance related to in vitro and in vivo correlation. This is how parameters such as particle size distribution, in vitro release of a liposomal product will affect the in vivo behavior.

Establishing product with regard to PB- PK modeling as a substitute to clinical studies for products where it's very difficult to recruit the patients would also be beneficial and in regards to talking about free, versus incapsulated drug, the liposomal product will be very useful to have a guidance of analytic methods for the determination of a free drug in such products and the parameters to be investigated and the validation expectation to be conducted.

Now, I would like to move to injectable and ophthalmic suspension. 0.5% however, there's complex products not approved and opportunities for research include. Understanding the controlling parameters of dispersion state, for example, Polly pair done, that govern not only drug absorption but also

stability and having an in vitro disillusion method for the ophthalmic suspension. Now, moving on to nasal sprays. Since the publication of the draft guidance, FDA's 2003, nasal spray guidance, the set of in vitro test remains the same in the most recent product specific guidance. Test says spray pattern, droplet size distribution, and plume geometry on the obstacle free space. So an opportunity exists for the development of new in vitro trusts with more relevant to anatomical, and now, let us discuss a few opportunities for drug device combinations.

For example, opportunities exist for connected devices for GX. An alternative approach for CEBE studies. Also, for a CFD modeling, this is wide LOI studied for liquid products and is a useful tool for the characterization of NBI, nasal spray and softness. However, little research has been done with solid products such as DPI and further research opportunity is recommended. Next, we would like to highlight opportunities in model reform drug development. MIDD is a topic well publicized and widely used in simulations by way of requests. Dr. Rebecca will speak more on this topic later in session 2A.

There are clearly many opportunities we see for the FDA to pursue more research on MIDD. There will be a further expansion on his public comment later in session 3. We feel aligning with other regulatory bodies and expectations and utility of this will be a good idea before research is initiated. In the next section, we would like to provide commentary on scoring in vitro and modeling tool for respiratory products. Since respiratory products are very complex in nature, establishing this is a challenge for product development. The position and absorption from different lung regions is very important to achieve local and systemic drug concentration. As of now, establishing correlation with available in vitro tools like deposition, bio predictive or discriminatory solution, with respect to local and systemic concentration is not so predictive enough to understand the performance and equivalence of the generic products. Some road map on an alternative tool such as modeling approaches to replace some of the in vivo studies would be highly appreciated. It would be a great help that some are established and use of modeling on respiratory products. Now, I would like to move to some opportunities for process modeling and automation tools.

While there's many in silico information tools to Bert understand the process, we're still required to do some of this

testing. Opportunities exist to understand FDA's expectation on user software and validation of them and stability modeling. And the research from FDA in demonstrating of these tools is beneficial so the potential of these tool KS be leveraged upon without having to do extensive protocol and analytic testing every time. Lastly, I would like to highlight some opportunities in the AI and machine learning space.

Exploring innovative tools for artificial intelligence and machine learning can be important. Can research be performed? As this helps to establish the framework for including insights into such data driven technologies into the regulatory submissions. Now, let's look at the science and research journey. Could there be opportunities to share information with the outcomes earlier in a more structured way with enhanced visibility and include more details about the research performed? Let's think about that. I would like to brainstorm with you some potential solutions for consideration. Notifications of when results are published in a special research area and if they're presented, where and when. Create and maintain a live data base of outcome and research as they get published. Could there be a dedicated event, virtual plus live symposium showcasing the outcome of the funded research and the ability to interact with the researchers? Could there be a data base of queue articles by product type, that could be reviewed and referenced by GX companies in preparation of correspondence, product development and presubmission meetings with the FDA. Now, I would like to conclude with some closing remarks.

Although some complex GX has come to the market in the last few years, a significant number are off patent but still lack generic competition. With more complex products on the verge of losing exclusivity and patent protection, it's important to achieve demonstratable progress in increasing access to complex GX in the U.S. market. US FDA is actively encouraging drug companies to take on the challenge of developing and launching complex generics and there's additional opportunities for further research and enhance dissemination and access to knowledge geared from this program which we can further enable a more robust ecosystem for advancing complex generic product development. Thank you for your kind attention and now, I would like to acknowledge my colleagues who contributed in the preparation of this presentation. Thank you, wishing you a great rest of your workshop and looking forward to the panel discussion on day two.

>> Maria, good morning, good evening, depending on where you're joining us today. We are the project managers helping to coordinate this year's generic drug science and research initiative public workshop. We would love to welcome you to today's workshop in hope you are enjoying today's presentation thus far and are excited for the rest of today and tomorrow. Please remember, if you have any questions for any of our speakers or panelist, please enter them in the Q & A box indicating the speaker or panelist you are directing your question to. Throughout the day, we will also be posting useful links. We want to mention following the workshop, the presentation slides will be available on our FDA website. Also, if at any point during today's workshop, you experience issues with video or audio quality, we kindly request you log out of Zoom and enter back into the workshop to reestablish. We'll be taking a morning coffee break and returning promptly at 10 a.m., eastern time in the United States. Once again, thank you for your participation in this year's workshop and we hope you continue to enjoy today's workshop!

>> Session two.

Good morning, welcome to session 2. This will focus on how a broader adoption of modeling by generic drug developers can over come their inclusive challenges that are otherwise difficult. Panel discussions about the practical integration model integrated effort will focus on the best practice for the development of model and past collaborates artificial intelligence and machine learning to support the objective management and assessment. Session two will have two sub sessions, sub session 2A best practice collaborative, master file packages to bring generic to the model. During this session, they will successfully incorporate model integrated evidence into their drug development program while describing the practical practice for developing the MEK NIS.

To facilitate the implementation of the model integrated evidence. FDA is seeking inputs from industry, academia and the commercial experts to further development this concept and support of feasibility of implementing this concept. This sub session 2A will have 5 presentations. Our first speaker is Dr. Rebecca who is a clinical scientist. Her talk will be on model for modify released capsules, development and validation and establishment for B prediction. Our second speaker is a professor of farm Coe metrics and this talk will be on research related model master files to establish the concept and details

for practical implementation of model integrated practice in -- submission. The next speaker is a professor of system pharmacology from the University Manchester. This is on moles that facilitate the remodel reusability and the next is David with a partner from NDA and his talk is the legal considerations on modeling, sharing and implementation of model master files. The last speaker of session 2A will be a director and his talk is on best practice to leverage model integrated evidence, model master file packages to bring complex generics to market. Without further adieu, let's welcome our first speaker, Dr. Rebecca.

>> Rebecca: Hello, everyone! My name is Rebecca and I'm going to present you a case study of the IVIVR model and the use of evaluation of the impact of disillusion rates on rates in veto. The opinions expressed herein are solely mine and do not represent statements or opinions of these pharmaceutical companies. In this short presentation, this is the development and use of the PBPK model for a modified release capsule. I'm going to emphasize best practices on the development of this and the opportunities I see for the use of the future.

First, let's focus on the case study. During the drug product development, we have to modify release formulations with different in vitro or in vivo behavior. This is not enough to establish the correlation according to the FDA regulatory guidance. We are thinking if it would be possible to establish regulatory acceptable in vitro, in vivo relationship using the PBPK modeling. The purpose of this -- change in the solution profile, consisted of three time points.

The first one being 25 to 45 percent of the drug dissolve indeed 20 hours. The disillusion method used as input consisted of 2 hours. Followed by ten hours in 500 millimeters of fortified buffer at PH7.2. Based on this work. This is more relevant than the first stage where the dissolution was too slow. The model was developed gradually. This was entered in the software. Then pharmacokinetic parameters were determined by the IV profile in the PK plus model. Since this time permitted. Effective perm ability is based on these formulations to plasma concentration profiles observed in vie VOE. This was used to simulate the formulations. The assimilated profiles matched those in the in vivo quite well. All calculated errors were below 10 percent and all individual prediction errors were below 15 percent. Thus, we considered our model as validated.

As mentioned before, this is set on the immediate release product but there was no literature or data available on this. There was no plasma concentration after administration of oral solution. Part of model optimization was the increase of gastrointestinal times in order to prolong absorption of the modified released capsules. The increase was still within an physiological range observed in vivo. In order to capture vulnerability in the parameters observed in vivo.

This is for a new formulation, with a different solution rate. As shown in the figure with red line. This hypothetical formulation has 0% of drug absorbed. The assimilated concentration profile is similar to the test product with a slight delay. Also, virtual clinical trials showed bioequivalence of these two formulations. Based on these results, the change in the dissolution specific is justified and accepted by the regulatory agency. What best practices we usually follow when developing PBPK models? First is gradual development of models. For example, first developing the model for intravenous data and then use the immediate release products to capture absorption space and lastly to include this. This shows it will predict the formulations, different strengths and different physiological conditions. With regard to the perm ability, after the administration of the oral solution could be available, it could be used. Other possible cases include data after administration of immediate release oral formulations, data after directed administration to different parts of the --

Thirdly, the bio relevant and in vitro method is necessary to be used so the model can discriminate between different formations. There should be at least two formulations with this to actually establish the relationship. What challenges we face during the development of PBPK models? Sometimes we struggle with selection of appropriate model parameters. For example, when there are multiple significantly different data for compound specific parameters one has to decide which to use, make some in house measurements or parameter sensitivity analysis. Also, with regards to population physiological parameters, due to high variability in the gastrointestinal tract, there's still questions which mean values and which vulnerability should be used. With regard to the inputs, it is sometimes quite challenging to find bio relevant and bio predictive solution methods for a non dosage form. Also, the perm ability and the variability of oral and non oral are not easily found and justified. When performing model validation, there's sometimes not enough data to properly develop and

validate the model. For example, none bio equivalent data. On other occasions, there could be a lot of data but significant study differences. This complicates the validation of the model, especially when trying to reach 10 or 15% prediction error. There remains this question of what prediction or error is appropriate if a specific model, for example, if the intention of the model is to predict the bioequivalence of the formulations in our opinion, it is more important that the model adequately describes the ratio between the test and reference formulation and it is not so important how we describe the absolute values of what you see observed in the in vivo study.

Of the challenges we face of development of the PBPK model is quite similar to the challenges using IVIC reported in a survey for 2017. In the survey, different parties emphasize the challenge with lack of appropriate clinical trial to be developed, regulatory uncertainty, lack of time, resources and skills, the prevalence of validation, complexity or lack of appropriate dissolution method and no difference in the in vitro release of different formulations. However, it was said to be frequently used as a tool in product drug development because it provides a better mechanistic understanding of the formulations. I believe in the future, we can solve these challenges. What is it useful for? There's a way, required by some regulatory agencies. There's been ideas to justify bio waiver for the BCS class 3 drugs with Q1/Q2 differences. It can also be shown to find BE approaches for non oral routes. The models are also used for justifying different scale up and post approval changes such as the case I presented.

In the end, I would like to thank my colleagues at NOVARTIS and globally for many scientific discussions about modeling. Here's the references used during the presentation. Thank you for listening. Please provide any questions in the Q & A box. I will also join the panel discussion.

>>Today, my name is Andrew and I want to talk about master files or model sharing and how it might be useful in practically implementing model integrated bioequivalence approaches for regulatory submission. In general, there's a great benefit of model sharing. I think it gives an improved reproducibility and validation of scientific results so that other people can take your model, and see what it does and actually see what the model is exactly. I typically run a course called models for biological systems at the University and one of the course components is to take a paper and try to

implement the model described there and maybe 85 percent of the time, some components of the model are not described enough that you can reproduce the model and reproduce results in the paper.

So sharing models could greatly improve that reproducibility and allow other people to validate your scientific results. It also allowing for knowledge propagation, a faster development of new science if you can take the old science, the models that have been developed and use them for new purposes. Furthermore, it allows explicit validation and verification of the models that have been described and used in previous work without having to extract and assume things that might not be said in publications. So how can model sharing be useful in things like bioequivalence studies? So here is a standard bio equivalent study where we have a 2 by 2 cross over design and then an NCA based analysis where you can look at AUC, C max, and then geometric mean ratios and see if they're within the specific limits for equivalence. And there's a lot of problems with these types of studies, potentially. You can have things like too sparse of data so the NCA analysis does make sense. You can have other problems with the data that make them inaccurate or biassed. You might have components of the drug like long half lives that make cross over designs not possible or practical. You might have lots of variability from different potential sources making it hard to run these types of studies so there's a number of potential problems with standard bioequivalence designs. In the last few years, our group has developed this in order to over come these problems. Using population PK models, we can look at sparser data. We can handle different levels of variation in a better way. We can handle more of the problems that might occur with NCA based analysis. The general structure of this bioequivalence method takes some bioequivalence data run and that has been updated from the reference model of the reference substance to incorporate and allow you to identify differences between test and reference products.

Once the modeling has been completed, then we use our models to evaluate whether there's bioequivalence or not. So our model is used to simulate what the other PK characteristics are in order to evaluate whether there's bioequivalence or not. Inherent in that is looking at uncertainty estimation from our models so we have to take our model parameters and use it to assimilate from uncertainty distributions in order to draw conclusions about our bioequivalence methods. These methods

have been shown for sparse data examples to control over one type, overall type 1 error. As well as a higher power than standard NCA based methods. That's especially when we have high valuation in the data and sparser data. The methods have also been shown to allow for reduction and study duration. Here, we have an example of long acting injectable products which might use a cross over state study in order to assess bioequivalence. In this, you have some reference product which you then look at a steady state PK profile and switch to a test product and then wait until you have come to steady state and then you assess the PK profile at steady state and compare. With model integrated approaches, one can look at PK profiles in this test situation before reaching steady state and then subtract what you have of the reference product in that profile. So research shows this approach controls type 1 error but will require, this compared to the cross over states study but it can be much shorter. For more information, you can go to this website where you see a presentation that will describe in more detail what is going on there.

So practically, what is needed for this? What we need is a model or a set of models so you may have previous models based on a referenced product or you may need to build a model in a predefined way. Currently we're working on model integrated analysis. And then you have to adjust these models by adding in, the effects, differences in the absorption characteristics across products so you can assess what the differences mean and whether the products are equivalent.

Furthermore, you need to have it identifiable given the study design data, the data you expect in a bioequivalence trial. Lastly, the models should be qualified. You should be able to predict what the AUCs and C maxes are for say the reference product. We advocate using posterior predictive checks for that. So if you think about what is needed for long acting injectables, you know, if you look at the long acting injectable products approved, roughly 33.

17 of those have models in the literature. 27 total models of these 17 products. And many of those models are based on multiple different studies in drug development so you have a lot of individuals, lots of different designs so components of those models are likely not identifiable in a simple bio equivalent study. So what is needed to be done is you add in these extra components that you need in the absorption phase to identify the bioequivalence or not. You may then need to reduce the model in order to make the model identifiable. And

then show the model can predict reference data in terms of C max and AUC calculations.

So that process, it would be very useful to have a repository that could store that information and take those models that have passed, that can be used for bioequivalence so other people can use them as well. So if we think about model repositories, I was involved in an EU consortium called DDMORE which developed a model repository. There's some links here if you want to check it out. In that model repository, there was currently 151 models ranging from PK models to PBPK types of models. It's publicly available, free to use. Searchable, supported by peer review so it allows qualification of the models although its only qualification relative to a published article about that model. And when this repository was active, then there was support from conferences like the page conference and publications that were encouraging or even requiring submission of models that were used is to be uploaded in this model repository.

It's not being used anymore. The last time a model was updated was about a year ago on the repository. So what can be learned from that experience? Well, I think one thing is that, the qualification should be for specific purposes. You could have a qualification based on what is presented in a paper or submission but you could also have qualifications so that you can use this model for example, for bioequivalence model based. You can have different levels of qualification, scientific panel approval or FDA approval. You could have, there's also problems with model repositories so with many models oftentimes the data or data structure is important in how the model is described. So you need to share some of the model, the data structure any way in order to understand how a model works. This is especially true with this. If you want the qualification, you have to pay for it as well. I think we'll talk later in this presentation -- in this set of presentations about IP issues and of course, people may have developed their models in different modeling languages. They'll have different file formats and maybe different types of data. So I think that model sharing can increase the quality of scientific work. And for model integrated bioequivalence analysis, a way to share and qualify models for specific products and situations will really aid in the practical implementation of the approach and make it more equal for everyone. I am happy to discuss in the discussion later on. Thanks very much!

>> Hello, everyone! It's great for me to contribute to this session which talks about model accessibility and using more wider modeling in bioequivalence. As usual, my conflict of interest will be available publicly as part of this slide set later on. This is slide is a reminder from four years ago and indicates that we have past the stage of if we need model simulation, but we're now discussing how to apply the modeling simulation. Modeling simulation helps us with many aspects including the translation of bioequivalence of healthy volunteer studies to different disease population as well as with the complex generics. Even in very rare occasions, we are having these differences, for instance, between different populations and so on but we can figure them out using modeling simulation and therefore, not all cases warrant clinical studies. This is another reminder from last year where we were talk about the modality of using modeling simulation. For many people, modeling assimilation comes with a specified modeler in the form of what I call toys for big boys. What we're trying to achieve is really, modeling for all in a way that the modeling becomes an integrated part of the assessment of bio stimulants and it's in this context that the reusability feeds into the discussions that we had last year on modeling master file.

Okay, what is reusability? This is the way that Wikipedia actually defines it. As you can see, the content is only related to the software and the reuser part of the code in the next set of the codes that you're generating purpose is considered as full reusability while if you are modifying some of that, and then using it in the next stage of software development, then that is considered as leveraging.

You can see at the top, that number one, this is work in progress. And not everything is fully settled but also, you noticed that this is only debated, discussed in relation to software code. Well, how reusability applies to the models? At least there is one indication in literature from 2013 that defines the reusability in the context of models. However, for the purpose of the research I'm going to share with you, we have to extend these and we looked into, not just full reusability which is a piece of the model that is basically reused in its entirety but we also considered partial reusability which is the same as leveraging that you saw in the case of the software. And also defined external reusability in the form of reuse of a model by a group of investigators that they had no links to the original group of researchers who developed the model as oppose to the internal reusability which

is the reuse of the same model by the group who had generated it.

The research that I'm going to share with you and the analysis of the literature is a follow up to the debate piece published in CPT PSP in 2021 which was one of the highest citations in that journal in 2021. All of the definitions of software, platform, model data, open source code, versus non open source code platforms are taken from that article and in this piece of research, we have identified 145 articles as original PBPK model development pieces and followed their citations.

The left hand side graph is the break down based on the platforms they were reported in this 145 articles that I mentioned. Over 1,800 citations made to these original PBPK model developments, however, fewer than 300 involve reuse cases. The results are summarized in these stark graphics and one thing to note is only 40 percent of the open source code platform cases were reused and to make the picture even worse, only 60 percent of this 40 percent reuse cases, is -- therefore, the number is open source code platforms of PBPK was 24 percent. The same information here is provided as previously slide with addition of the time trend in the use of each of these platforms. Here is another way of looking at the data with the color code that separates between the open source code platforms versus non open source code with the hashed area indicating the platform that switched from one format to another in 2016.

Here are the individual break down for the two non open source code platforms. You can see this here, the numbers are based on each of these software. The reuse cases are as I mentioned earlier, were much higher than the open source code and also, the external use was very high at both. In contrast, the most popular open source code platform used for PBPK are not showing signs of high reusability with 19 percent and 25 percent in each of these two cases shown in this graph. When we put all of the open source code platforms together, this is the picture and the numbers are summarized, 54 percent of the reused cases were external and 12 percent of the reused cases were involving full reuse case.

Inned second part of the -- this picture is showing geographical distribution and as it is evident, the open source is open in this, rather than the U.S. so the time trend for the areas, the application, indicated a much diverse use of

these platforms in different areas as oppose to the first ten years in this year. However, in the recent year, toxicology absorption and animal PBPK dominated the application areas of open source code platforms and clinical pharmacology was a small piece. More options of platforms have been available if the recent years for the PBPK modeling within the open source code platforms, however, it was not as equally distributed as it used to be ten years ago. Industrial applications of open source code platforms for PBPK even after combining with the regulatory was a quarter of what was used in research organizations and academia. Certain platforms were preferred for certain areas and there were rare occasions that one platform was used broadly in different areas of applications of PBPK.

Moreover, the impact of returning from charge to free was investigated for one of these platforms against the overall trend in the general use of PBPK and it was indicating that possibly, making this platform free has had some impact on the higher usage. In general, the PBPK applications with open source code to platforms was dominant in the area of toxicology and also, there was some local preferences, data not shown, for instance, in Germany for a German product, open source product and similar trends were also observed in Japan.

This is my final slide. And before offering the points that I would like to be a part of the panel discussion, I would like to acknowledge the unpublished research work by HKA at the University of Manchester. The point I'm offering for the panel discussion is a debate on misplaced emphasis that was put on open source code platforms in several of the grant applications offers. I believe the emphasis should be on quality assurance and reusability of the models which are not in fact in favor of open source code platforms. Multiple factors determined external reusability of all of the different models and some of them are subjective but some others are objective options that are related to quality support and the structure that are in place for reuse of these by a wider group of modelers. Increasing the reuse cases, is an urgent need and of course, historical data and FDA can play a big role, however, not all of the data would be available for such modeling and whenever needed, such data should be generated. With that, I would like to thank everybody for listening.

>> Next session. Good morning! My name is David and I'm a former FDA division director and office director in the office of new drugs and I have been asked this morning to make some

comments on the legal considerations of model sharing and the implications of being able to place that information in model master files. Now, master files is an interesting thing and it's largely for the purpose of protecting the confidentiality of confidential information, one type of which is trade secrets. When you look at intellectual property that relate to drug, patent, trademarks, FDA granted exCLUS IFT, all of this is transparent once granted. But what is unique about the information in a master file is that the information remains confidential and known only to FDA and the people who submitted the documents.

So my focus is going to be on can we make the case that we can protect modeling and modeling systems by declaring they're trade secrets. Trade secrets are interesting. They evolved out of State common law. Out of property law. Trade secrets were considered the property of the person who created it. Lately there's more federal laws that involve trade secrets and we'll look at how it's discussed in the food, drug and cosmetic act.

But let's start with the most common definition of a trade secret. In a certain characteristics. Proprietary information that a company or individual uses that has exclusive right to. So first, it has to be genuine and not obvious. Something tangible. Something created. FDA is very explicit about what kinds of things they mean by this. Second, it must provide a competitive or economic advantage and have value to the owner. And notice that's in the present tense. So something that you no longer has value, no longer trade secret. And third, it must reasonably be protected from disclosure. So if we boil it all down, it actually is in the title. It has to be relevant to trade. It has to have value to trade. It has to be something that is commercially valuable. It has to be a secret. We find references to trade secrets in reference to the food, drug, and cosmetic act. There's a prohibited act for a person who works for the FDA to sort of shorten this long paragraph which is even longer in the act, any person revealing a trade secret which is entitled a protection. There's penalties defined in the federal criminal statutes. It's a little unusual as a prohibited act. Most prohibited acts are things that manufacturers can't do but this is something that an FDA person or advisory committee member cannot do.

The code of federal regulations expands this. We can compare it to the common law definition of a trade secret. So a trade secret may consistent of any commercially valuable,

that's the same so it matches, plan formula process or device, so it's very specific. But I think by saying formula or process, that would include modeling. That is used in the making, compounding processing of trade commodities, okay, so it's evolved in preparing, making decisions about how to make a drug. So that works. And can be said to be the end product of innovation or effort. So it has to be innovative or substantial effort. That's back to the common law worrying. It shouldn't be obvious. And then there must be a direct relationship between the trade secret and the productivity process. Is the modeling used actually in the drug approval process?

I think the modeling fits this pretty well. And then they go on to say, that data and information submitted or divulged to the FDA administration that falls in the definition of a trade secret or other confidential information, but falls within the definition of a trade secret is not available for public disclosure. So full stop. FDA says, trade secret, we won't disclose it. So what pushes back on this? Another law. The freedom of information act. But the freedom of information act which requires the government to actually be transparent about applications and documents and so forth has two important exclusions. The one that relates to manufacturers is it doesn't allow disclosure of trade secrets and the one that applies to FDA is it does not allow FDA to disclose internal deliberate process documents, like e- mails, draft reviews or an internal evaluation of master file. This would not be dis closeable under FOI.

There's some interesting court cases. There was a lawsuit that made the case that when an IND is abandoned, the information from that no longer commercially pursued product should be made available to everybody so that everybody can learn from that. But the manufacturers made the case to the court that just because that particular molecule is not preceding, doesn't mean that the information in that application is not commercially valuable and it's still commercially valuable even if the product would never be sold, but it's still a secret. The courts agreed. So it's pretty safe. It's complicated because they're big documents and there's a lot of information in those documents. They're not trade secrets which is why when you request an application, you can get a redacted version that has the non trade secret information.

When there's a request to release it, the company can

identify the trade secrets and say what can be disclosed and when can't. There's an act that requires federal agencies to ensure the quality of the public information that is disclosed and this doesn't have a lot of direct baring on master files. So when we look at the methodology and the validation of where the locations and when are the options? Obvious two are public and confidential ones. It could be in peer review literature. There's quite a bit of that. Some of them put appendixes on the web that might have source data or code but it's not as detailed as you would find in the typical FDA application. There's web publishing. With raw data sharing. NIH has information on raw data sharing. There's a lot of methodology located here, but it's all of the methodology confidential to FDA and when you think of the validation and verification from assays to validation of statistical methods for clinical trials, there's a lot of information that is not disclosed, embedded in these and the master files is a location where if you want a focused data set that really honed in on the issue of a modeling information, I think it would be perfectly legal to put it there and for the FDA to not disclose it.

What are the issues? One is, there's an owner of the master file. So if someone wants to use it, they have to actually get the owner's permission. They may have complex relationships with other companies and there may be conflicts of interest. What makes the master file a trade secret? Is it a method? Is it an algorithm? Is it a unique data set? What is the trade secret? Is it software? Is it validation data set that was used for statistical modeling that itself was public and the algorithms were not? Who verifies the use? Presumably the FDA, the way they do when they evaluate the master files. How does FDA track the master file with modeling information and considers it invalidated? Would it be publicly available in an FDA review? The FDA's own modelers are fairly good at publishing their modeling results and their thoughts on methodology. Does the master file block that in some ways?

What exactly are the boundaries of the trade secret? So in conclusion, the whole purpose of master files is to store secrets. And it could do that very well if and part of what is necessary for FDA to think through it, what is it they think is best kept in a confidential matter? It couldn't be as transparent as public domain information? But it could reduce the redundant validation work and provide more detail than the published literature. Thank you very much.

>> Hello, everyone! I am the division director of CDER @ FDA. It's my privilege to talk ABLTH best practices, leverage model integrated evidence and model master files packages to bring complex generics to the market. There are mainly four areas in regulatory science and research to support generic drug development and approval. Model simulation is indispensable part that plays a pivotal role in all of them. Model integrated evidence references using MIEs such as the refers to the model generated information such as the virtual bioequivalence study results in information. MIE has had an increase in value generation for improving high quality generics. At the same time, it comes with challenges and opportunities. Challenges include knowledge, technical barrier as a result of developing an ecosystem from the generic drug industry as oppose to the new drug industry. In practice, models with high complexity face the complex challenge of model standardization. In many times, existing data to verify and validate the so called model, can be minimal, or does not exist.

Generating data for model can also be time consuming and costly investment. Once a model has been developed and received sufficient model benefitting, it can become a perpetual, intellectual property that is shareable across products with different formulations. For those who have received the regulatory acceptance, they can potentially exist as model master files that can be reused for the same purpose. Before we discuss model master files, you can appreciate a list of nice characteristics associated with the drug master files.

For example, DMF holders can authorize one or more applicants or sponsors to incorporate reference information contained in the DMF without having to disclose that information to the applicant sponsors.

For DMFs, they do not have to be reviewed. In comparison, DMF can be viewed as portable, reusable, general risible assurable models as well. For potential model files, not every model will need a master file to be shared. Certainly, we may not want to give rise to operational -- here. Generally, models that are challenging to get proprietary information and that need a larger data set from other sources, may benefit from having master files. This gives the least of such models as well as models that can be easily duplicated from scientific publications. For those that can be easy to duplicate it, we may not need the master files.

What are the benefits for model master files? First, it can serve as a communication tool that will bring public awareness of the utilities of the model, acceptance uncertainty models and the steps to validate a model with sufficient details. It can certainly have a cost saving for both industry and the agency. It can support the standardization of model building and model V and V. In can have the current status quo for the particular model development and serve as a benchmark for further model advance.

Currently, there are many models that can be critically used for drug delivery and assessment. PBPK models for locally acting products, PBPK models for oral absorption and quantitative, clinical pharmacology models. The successful application of a PBPK modeling for acting product approval has been shown in the case of this drug approval. The product was approved based on a totality of evidence based on the leveraging the simulation instead of comparative studies in had patients. The modeling approach demonstrated the BE between the generic reference products and the presumed set of action by characterizing the relationship between systemic and local drug exposures. The model process involved assessing the goodness of fit for observed data of the concentrations in skin tissues and plasma. Of note, the model also includes the overall performance of the model platform for predicting local and systemic relevant products following the same drug of delivery. The case serves as the example of using PBPK modeling simulation for V and V assessment as well as providing example for good practices of model V and V model drug products.

For the second case, this study included considerable amount of censored values in the response which are the PC20 data. Model based data has critically contributed to the approval of the generic version of Albuterol sulfate inhalation. This approach with some scientific analysis improves the model provided integrated evidence to support its final approval as one of the first generics in 2020. This likelihood based modeling approach performs the data can represent a good practice when appropriate substitution arises.

For the third case, for the topical product, this is comparative clinical end point BE study showed for task reference and priority of task to placebo. However, the study failed to show reference to the placebo. The modeling simulation approach -- based situation. Simulation for this, the risk is low and abridge the study regard -- the measurement. (Inaudible).

For the fourth case, the modeling approach has been used to assess the impact of the division in particle size distribution between task and reference products. Based on the PBPK model development for this particular product that has been sufficiently verified and validated, simulations have shown that the chance to observe this, to lead to the bioequivalence is low. Consequently, the PBPK modeling is not supported is the tentative approval. We believe the same practice can be applied to this and other products when facing similar situations. In the end, my presentation is mainly to stimulate the further thoughts on qualifying models that have been accepted by the agency into model master files. With the arrival of the model master files, we can make this regulatory users models publicly available and enable the playground and lower the barrier to use the same or similar practices that all stakeholders, especially for the under privileged, smaller or mid sized companies. Particularly, we would welcome further thoughts from the panel on the list of questions like how to define and share MMFs, how to deal with proprietary information, how to take business interest into account. With that, I would like with all of the simulating presentations, open the panel discussion regarding the future modeling investments to bring the best of practices and model master files into practice.

>> I would like to take this moment to introduce some of our speakers to the panel.

Without further adieu, I would like to start the panel discussion. I would welcome all of the panel members to open their camera if they haven't done that yet. And as we communicated, I would like to start from three questions. And to go around the panel to see voluntary comments for each of them. After that, we'll go through some spontaneous questions received from the audience. And based on that, we will summarize all of the discussion at the end and close the panel discussion.

The first panel question that I would like to seek all of your input is, what do you see as the critical components of the best practices when implementing model integrated approaches to support BE establishments? What is currently (inaudible). So if you are willing to contribute to that question, feel free to open your camera to jump -- to unmute yourself.

>> YU: Well, I guess I can start. I think a clinical component is to improve the creditability of modeling and simulation. I feel, published PKPB data, for the drug developers and there could be a situation where you have to develop the parameters and with the use of different PK parameters, you could get different modeling simulation results. So this could create doubts about the use of model simulation. Another potential use is the use of different software for doing modeling simulation. As you know, if different software could have different set of systemic processes or different assumption of systemic processes and parameters. Of using modeling and simulation to have proficient, the type of systemic parameters. And the use of the type of PK information, that is useful for pursuing drugs. That's my opinion on the first one.

>> Let's take turns to address.

>> Carl: Was this a question for me?

>> Yes, Dr. Peck, I see you unmuted yourself. I guess you want to address this question.

>> Dr. Peck: Well, first of all, thank you for inviting me to this panel. This is great. From my point of view, a critical -- well, several critical components for best practices would include fully educated personnel that is to say, you know, industry and regulators need to understand this approach and be aware of it and be fully in tune with what the assets and limitations of model informed evidence would be. Second, user friendly software. Software that can be understood by the expert and understood by the non expert. Informative diagnostics would be an important element of the computer programs so that it can be sure that the modeling that you have done, you know, it meets the assumptions underlying the models and that they are true to the data that is being evaluated. And finally, obviously guidance and template for submission of this information that would be standardized so that reviewers and submitters would understand exactly what the requirements are.

>> Thank you!

>> I think I can go and just endorse all of what Dr. Carl Peck said but I will dive into some of the details with regards to the suggestions and recommendations by Dr. Peck. Going back to

the first comment, particularly talking about the software creating the different results. My experience is that in all of these cases, there are a lot of country intuitive, I would say, things when we go and look at the data rather than actually making up the perception on the basis of what we think there are with these scenarios because for instance, that was also our belief that the impact of the software would be really great but when we looked at the bio simulation which was as part of the European, actually, grant IMI that was running for five or six years published by Allison and Adam.

The outcome was indicated clearly the differences coming from the different software. They are minimum compared to -- it wasn't the case there is no differences. In some cases, yes, there were differences but they were minimal compared to the impact over the modeler. So when we say with software, we have to be careful. I think what Dr. Peck is saying, is absolutely true! We have to focus more on the modeler and their understanding and the making of the assumption changing parameters that they should not be changing in every case and so on. And the same with regard to the widening. While everybody's perception including my own is the open source code will basically encourage everybody to go and use it bigger. When we look at the overall use cases, you know, a few years ago. We noticed that is not the case and recent data I showed you, when we look at the reuse cases, it is the same. It seems that the open source code does not have the same traction with regard to reuse for whatever reason. We have to analyze the reason and we haven't been able to go to the next step and analyze. I will warn people against making perceptions before having data.

Many of the data we are gathering, they are completely counter intuitive.

>> Yes, thank you! Regarding your comment with open source, since we're putting effort to make codes and research outcomes available to all of the public, would that be because of lack of user friendly interface or lack of confidence that the agency would accept the open source based modeling simulation outcomes? Because of the commercially available software, they do have -- in the past that gained FDA recognition? That naturally brings up the concept of a modern master file. Later on, if we can broadcast a certain utility model has been accepted by the agency, then it doesn't matter whether it's open source software, by using the commercially available software without it? Would you agree with that comment?

>> Yes, yes, fully! You know, the transparency for whoever is assessing and the create- ability, they are definitely without so nobody argues and disputes that but who should be actually be in that position to see, going become to the legal arguments that were discussed with the talk. That is the issue. We don't necessarily need to make it open to everybody. It is true that open source code and I have declared in my publication, it's very good for scientific research because it enables us to reproduce change, et cetera. But when it comes to reuse, particularly with the small companies that you were talking about and they won't have the specialized modeling in many cases, but you know, they will go more in favor of something that is less risky.

>> Thank you, Amin. Rebecca, please.
>> Rebecca: I want to say something about best practices because it deserves some point. I want to emphasize in my presentation, what I would like to emphasize now is that we are still like the generic industry is missing some -- I wouldn't say guidance but some guidelines from the agency with what would be appropriate validation characteristics for different models, for PBPK and also, model assessment and everything because there's no, especially for the second part, there are no published cases on what would be the regulatory acceptable and with regards to PBPK modeling, I would say we have many problems with the validation of modeling using different formulations with different in vitro and in vivo. They don't always have the non bio equivalent data to validate the models. On the other hand, there may be many data as mentioned with different in vivo results showing in different studies significant inter study variability and how to coordinate it into one single model to show it's validated and useful for this purpose. There are some struggles. I don't have the answer on how to solve them but this is something that needs to be addressed.

>> Thank you, Rebecca! I would also like to mention from this early morning presentation, you know, in the center, there's huge opportunities of the people presented by using modeling simulation in the generic, but I would say that it's shared a responsibility, the responsibility shared expertise to bring this aspect to implement the value of using the modeling approach. Certainly, FDA following the workshop we are diligently taking into account of your inputs, your valuable inputs and comments into our future research focus efforts. However, I would say there is still some areas that the best of

practices still face a gap to be implemented like for the orally inhaled drug product and everything. And with that, it naturally goes to the second discussion question. What research areas should the FDA invest in to support the best integrated model for the development and approval of the complex generics. I put a list of ones for your consideration. For example, long acting injectables, orally inhale products. Here, I would welcome your further thoughts on them all or if there's an area that has been left out of the equation, certainly this is the best value to have your input and comment.

>> So first of all, thank you very much for organizing this workshop regularly. It is a burden for educating us and coming up with a strategy that will work for all of us. I have a few commented related to one and two. First of all, I want us to take a step back and appreciate where we are. I want to paint a more positive out look. We're in a position here unlike where we were twenty years ago dealing with frequent model approach for data approval. It's not a different question. Back then, could we use model bass approach to approve a new drug? It's not different than here. It is similar but I'm happy that we're discussing it among clinical pharmacologists. So that's already 90% of the battle that has been won. So with that positive attitude, I think what would benefit the industry, the pharmaceutical sponsors is going to be, if you take the two or three different methods, one is your modeling simulation versus something which is PBPK and maybe, another approach. What might be the like three to four or five steps for each of these approaches that you expect from the sponsors to submit the meeting requests that would be most useful?

And for example, there could be, you know, just whether source of the model or the parameters or performs such and such. We want to document how you validate your model. So rather than be prescriptive, ask, have some communication what you need to justify what is useful. Second point is flexibility. As a field, we're at the cusp of taking off and making, bringing a model informed bio, to a more scalable paradigm, right? So that requires flexibility. If we're having too much of prescriptive data like guidance and such, the guidance can be flexible too. We will only in my opinion, slow down scientific innovation because there's some parts that still require research and there has to be that flexibility given to the sponsors. Having said that, I also see a challenge comparing to the new drugs part. The generics like prescriptive, I think, at least my limited knowledge, of

generic pharmaceutical companies really like, okay, tell me you want me to do one, two, three, I'll do it. I'll give it to you and then we're done. That's a cultural change, nothing to do with science.

That can come only through sharing success and this is only what we can do, you can blind the data and the product but maybe, if there's ways these forums are other confidences, that you share success of how is my BE used to make additions and how you thought about it. It's the thought about what did you look at and how did you deliver on it? Those will go a long way. Those are my three comments.

>> Thank you! This is really important, I think, your call for generic industry scientists as well to join the effort to be more initiative, and to develop the implementable modeling tools. It's really, you know, our class. So I see another speaker wanting to share their thought on the industry perspective, can you share your thoughts, like what research area that can benefit industry overall, we'll be greatly appreciative, thank you. Your turn.

>> RAJA: Thank you. Hopefully you can hear me well, I just wanted to go quickly on the first two. I thought we can continue -- well, everybody is asking for clarity on modeling. So we can do that. Basically if the FDA wants to work on the tables, with respective to the programs and software you use, some kind of a basic validation table or model that you need for acceptance of the ANDA, we can start creating that like, say, maybe one or two three days as you need. So that will build the clarity on the people, what is needed for the application. And then the other one is in the product specific guidance, you can actually just state where you can accept modeling as a tool for design or acceptance. So then people understand, okay, the modeling can be done to that aspect. And then the reference to the basic modeling either like I had mentioned before, either the appendix or as a reference from some guidance or some publication, I thought that's a standard approach we can do.

For the second question, we talked like, we had to establish there's two things here, right? There's the mechanistic modeling and population modeling. So for mechanistic modeling, I see more research to be done to have the in vitro methodology that is bio predictable. So we need to work in that area for sure. On the population PK, we need to have where you accept the current data as an uncertainty or

certainty of the model that you accept for this simulation for the, you know, for the B purposes. So these are two areas we still need to clarify for the agency point of view so the people understand. So what is the acceptability of the current model to fit the current data so I could use this model to go and establish this definitely. So where I cannot do the studies, or the B studies where we have some problems in establishing the BE because of the high variability type of things. So these are two areas, thank you.

>> Thank you for those valuable comments. We have a note taker, someone who is summarizing. I lost track of the sequence on who raised their hand first but I will call Andy first. All of you raised your hands.

>> Andy: Thank you, I want to reiterate what he was saying about trying to avoid being too prescriptive in talk about the standards we need. I have heard people say we need a standard and a process to describe what needs to be done. You can have standards and processes that describe the modeling term, if the modeling terms, what is sort of the basic things that need to be demonstrating when using a model for the bio equivalent studies. So what do you need to demonstrate in your models can do and are there specific types that you need to demonstrate, you can maintain a type 1 error or when you can maintain the say, type 1 error. Sort of minimally, the things you must be able to minimally do in order to do the modeling exercise and then after that, maybe, having a descriptive process that says what was done and then people judging it, the regulators and making sure we can trust the results makes a lot of sense. So what areas does FDA need to research further? I would say using models in ways that make sense that when you're uncertain. So investing more in the uncertainty of what your models are telling you, as well as using that uncertainty to make decisions. That is my area that I think is important.

>> Thank you! If I summarize your point, it seems like the computational aspect, like the template for error control is worth further development from the methodology side. Also from the research barriers, whenever there's uncertainty, the modeler doesn't feel comfortable, like skin penetration. If there's like a process and we're not keenly clear, then we need to investigate further. That is certainly being extrapolated to other areas wherever there's uncertainty for the drug development field or select of data to support, certainly we can invest in those areas.

You know, can we welcome you for further comment? Sorry for me?

>> Yes, so I comment on the second one with respect to the different research areas, I agree that it's useful to develop mechanistic model to correlate in vitro release data to in vivo performance. But that takes a long time and a lot of effort to accomplish, to produce a useful outcome. Generic company needs quicker assistance from FDA. You know the recent product specific guidance for system level -- which is a product that requires five years application. FDA actually has specific guidance which recommends doing a bio equivalent study after one year of application and they validate that the sign using modeling simulation. I think this is a good area where FDA should welcome more to develop quicker help to generic companies to allow us to perform shorter studies for product long acting injectables that require demonstration of bioequivalence of a steady state of patients and that could take many months to years to accomplish.

So if we can use modeling and simulation to develop design to shorten the bio equivalent study, that would be a lot of help to a generic company to provide an alternative to patients. So I think this is something that FDA should spend more effort on too, in addition to mechanistic modeling.

>> And then there's opportunity for us to use a model integrated approach to propose to come up with more implementable kind of -- regulatory pathway for high cost savings. Absolutely! We can truly invest on those areas.

>> Well, I have a couple of comments on the research priorities. I want to pick up on a comment that Apotex he made during his presentation is the pesky outliers, the extreme values that can wreck just ordinary two, one sided T test analysis. We definitely need a way to both, not ignore those outliers but to incorporate them on an intelligent way. So I'm going to embarrass you and just let you know that, you're leading a research effort within FDA and with an external researcher to evaluate non informs base, using the T distribution to deal with that for a non complex generic.

Finally, I want to pay attribute to a great contributor to the domain of research in bioequivalence and bio availability and that's LASLO, who we lost a year ago. In that respect, there's a memorial conference in Athens, Greece in October, 3 and 4 of October. It's going to be entitled, classification

and virtualization and anything in between. So I'm on the scientific advisory committee and I invite everyone to tune into that virtually or making a contribution to the current research in bioequivalence.

>> Thank you, we definitely need to celebrate the contributions from those in our field, who have directly contributed to the field on certainly a calling for more in this area but also, we need to recognize the contributions from the past, thank you for bringing it up.

>> You can hear me, right? I want to take an opportunity to thank all of the participants and the panelist in giving us a lot of information to think about and see how we can implement those going forward. One of the somethings which are kind of striking me, you know, in a lot of the people, a lot of the industrial people are looking for case examples or case studies.

Some of these case studies obviously can be imperially developed and probably we'll have publications around it. But do you think there's an opportunity to replan and run case studies on established models and software so that you can actually run through the case examples, P plan and then also, define what is the minimally required and what is the flexibility that we are looking forward to in other subsequent products. And tools that we're using because we have to remember, this is sort of a -- although a model has been used or a software has been particularly used, it is a continuum. It is not a static sort of one time incident you just put in the PSG on the shelf and you just take it off the shelf and use it. It's more about the continuing improvement and use of different assumption and the model and the parameters that will be needed for a specific product or a variation of the specific product because ultimately we're trying to figure out differences between the test and the reference. I will stop there. If there's any comment on that, we'll be very interested to hear. Thank you!

>> Thank you! I see a raised hand. I'm not sure if you want to respond to this question but if you would please say any comments on the table.

>> David: It may be related. One of the things that strikes me is there's an opportunity for FDA to use some of the forum that it uses historically. I did a quick search to look for something such as good modeling practices. We have good

manufacturing practices. I think there's useful documents like the ICH document, E9 that is heavily statistical. And I think there's kind of a spectrum of things from modeling to actually identifying the statistical methods that solve specific problems and that may be one way for FDA to develop a data base of tools that identifies what problem you're trying to solve. So for example, if the bioequivalence margin seems to be very wide and driven by within the subject variability, well, FDA has published a methodology on how to do that and it involves collecting more data but that's something not model based but you might think about developing a data base of scientific questions that come up in the review of generic drugs and what are some of the methods and tools that have been used to answer that.

That, you know, it also reminds me of something that has been used quite successfully at FDA which is coming from your colleagues which is the question based review practices where you walk through a series of questions and answer those questions but you could also annotation those questions with approaches to answering those questions.

>> Moderator: Thank you! I would recommend any further comment, either stand alone comment or in response.

>> Raja: One item we did not capture is the harmonization effort that we can have through the PKPD modeling with the European organization or other organizations and membership is using the studies. I said, we can also see if they accept the UCR data in Europe. So we really cannot do two clinical studies for the same model. Let alone, we cannot even afford one study. We're arguing that we cannot even afford one study and now we're asking whether we can do for each reason, a separate clinical study. We really cannot. So as the industry, we had to come up where a group on how to mutually recognize the data. And then we can have, like, say, 1, or 2. And then we can use modeling to support that. We support this, okay?

So we can use some kind of a philosophy in that state. We can have some mutual agreement. We can do one clinical study, therefore, we can extend it through the modeling through the other regions. That's something you should consider in doing such. Thank you.

>> Moderator: Thank you, Raja. I think that has been heard earlier in the morning as well. Certainly we have taken note

on that. There is also an assay process. If you have a comment application to both, EMA and FDA, you can take advantage of that rapid process as well. I wanted to mention that. Given the time, we can spend another ten to fifteen minutes on the third question and then entertain some of the questions received from the forum. So the third question, is if we can read. What could be the priority areas, investment needs and other considerations when using model master files to support the best practice for model integrated approaches? I heard many needs like model standard and clear thought from the agency on what can be used to validate the model? Certainly we have heard about that but I also want to further comment on the priority areas, the potential investment need on using the model -- I think the model master file may be a good solution to meet all of these needs.

I mean, please, please unmute first.

>> Amin: Sorry, I was double muted. Hopefully you can hear me. A couple of comments on this. I think, you and me, we have discussed this but for the benefit of others, I believe that number one, when we're talking about the simpler models, versus the complex models and let's say, all generics cannot afford these big models, but the assumption here is for every single case, we are going to make a big model. That is not true. In fact, the return on investment of making a bigger model is higher than a smaller model because once you build the big model, it's going to be reused, again and again. That's the whole idea. Once you build it, you can go and reuse it. For every single case, it's possible, but for every single case, you have to go in and do it separately. So that's one element. But the other element in regards to the presentation, there's several items and she emphasized when she commented but they had to go revise the model in this section, that section. I think there's a part of the, I would say, distrust, sometimes, in people, other people, and other modelers and modelers are those modifications that they are not in advance, sort of declared. That's why we're doing it and why they should not be constant going from one study to another. Of course, when you have the formulation dependent excipient, et cetera, all of them justified and you have in vitro data to support, et cetera.

In short of the system parameter which we believe is nothing to do with the drug and always represents the system, can be in every instance, actually changed, that's puts a little bit of a doubt. As you know my view on this,

understanding the system parameters they're defining the bioequivalence variability and in passing through sort of the window that we have for that. I think this is essential part.

>> Moderator: Thank you very much! I appreciate your statistics on the model reusability and rate. I think that, I think we need to constantly look at that. Great presentation by the way. I wanted to use this chance to thank you for that. I can see a hand raised. This is also in his area of expertise. Do you have an additional comment on this? I really appreciate your forward looking presentation in terms of proprietary information, on how to, you know, categorize that information on how to form the process perspective, you have worked with the agency for a long time. Really, how very insightful the proposals and comments are. I would have loved to hear from you more.

>> David: Thank you for those kind words. I think you can begin using the master file definitions that already exist in the regulations but a number of things that have been discussed, such as making available public information about the availability of master files or who might have used them, things like that, would probably require using a unique master file for this particular use. I think the assumption, a lots of master files is there's no need, for example, for the manufacturer to know the detailers of how container closure is manufactured, the equipment and raw materials and things like that. That can remain a trade secret but here you want trade transparency. But there's nothing that prevents you from defining a new type of master file. One interesting comment that came up in questions, is how do you ensure they're up to date if there's no learning about models? About a specific use of a model?

Or a limitation of a model how is that kept up to date? Currently, many applications have requirements that you provide updates. There's no reason you couldn't propose that. Now, that would take rule making and rule making takes too much time. But you want to go fast, well, it could take a lot of time but there's no reason you couldn't use it already and already with the disclosure of information that is requested, you can disclose anything with the permission of the person whose trade secret it is. I would encourage you to start with the existing system and then, learn what it is you want to modify about it. And then, tap our friends on how to change it in the regulations.

>> Moderator: Thank you, David. I just noticed our time is not what I had been thinking. That's my fault. On my part, I thought we had a lengthier panel discussion. Actually, we have to close this session and proceed to the next session. If we can communicate offline, that would be great! Thank you, thank you for your flexibility. So with that, I want to thank all of the panel members for your outstanding contributions to the topics we have taken note. We may funnel the thoughts later on through meeting proceeding reports and certainly all of your points will be critically evaluated. With that, I want to also say sorry to the audience. We have captured your questions and we'll also follow up later on with you regarding the proposal of things. We also have a way to convey your name to CRCG for sure. We will proceed to the session 2B. Lucy will be moderating session 2B. She's the deputy director. I will pass it to you for an introduction.

Welcome to session 2B. The application of machine intelligence -- to generic drug development and assessment sufficiently advanced, with the implement of these tools are fully enhanced, the efficiency of the generic drug development and assessment thereby, potentially reducing the time, cost, and risk. In this session 2B, we have two presentations. The first is a team lead to talk about entitled, leveraging artificial intelligence and machine learning to support directory efficiency and current progress. The second talk is with a team lead -- and her talk will be entitled digital twins powered by machine learning for realtime pharmaceutical R & D and manufacturing. With that, I would welcome our first speaker.

>> Dr. Meng: Hello, everyone! This is artificial intelligence and machine learning for the support regulatory efficiency. In this presentation, I will talk about leveraging AI and machine learning to support regulatory efficiency and current progress. This presentation reflects the views of the author and should not be construed to represent FDA's policy. What is artificial intelligence, AI? According to John, one of the founders and discipline of AI. It's the science and the engineering of making intelligent machines, especially intelligent computer programs.

Commonly speaking, machine learning is a sub category of AI. The recent decade has witnessed the exponential growth of AI. The AI is transforming our daily life, such as ATM, smart

phone, autopilot, chat bot and personalize recommendations. Given the prevalence of AI, we also see the opportunities of AI to facilitate the generic drug, development, and regulatory assessment. The first aspect of AI can help the development of automation tools such as for streamlining labor intense tasks with automated process, we expect to see enhanced efficiency, improved consistency and high quality deliverables.

The second aspect, we see the benefit of using AI is to borrow recently advanced DA analytic methods. These technologies can be used for promoting this, by promoting optimizing business process.

Meaning is there any pattern that AI models can be applied to realize the automation. The third is the AI, both domain knowledge and in- depth understanding of AI model candidate to achieve the best cost effectiveness. The last one is how to deal with unstructured data. For example, free text and uncalculated data. This part of it becomes the bottleneck for the whole AI project. Which often has no routine to follow and requires a lot of creativity but also bring a certain level of uncertainty for the project.

Here, I would like to share some experience, challenges from one of our ongoing projects. The ongoing efforts is a contract focusing on applying text analysis and machine learning to facilitate a specific guidance development. The left side diagram displays high level thinking on this project. According to our analysis, to develop a regular PSG for immediately released product. A developer usually spends 50 or 60 percent from public or intern that data sources such as drug labeling. And uses 20 to 30 percent effort time for information summarizing, for example. Generating summary paragraphs for a document. Based on all of the collected information, the developer will draw conclusion and recommendations. Given the current advance in natural language processing NLP model, the project team is working on streamlining the information we trivial and the information summary part. If finally succeed, a significant amount of time and effort will be saved for the PSG developer so that more time and effort can be invested on the human intelligence involved tasks.

Meanwhile, the project team works and is facing a few challenges including first, evolving layouts of source documents. For example, drug labeling and the internal review documents. Second, need for information retrieval based on cementing the understanding. Third, capturing the information from unstructured data. For example, review analysis comments

in the review documents and the last one, choosing a proper NLP model. For this project, one specific task is to extract paragraphs with ADME information from drug labeling. However, in some drug labeling, key words searching doesn't work. This is an example of a semantic understanding based information retrieval from drug labeling for full effect. The two labels as shown here contain no key words for food effect paragraph. Although the word for food appears in the paragraph. Using keyword searching for food, will lead to a high false positive rate.

The NLP algorithm has been applied to implement semantic understanding based information retrieval. We are now able to correctly label the paragraphs with full effect information in drug labeling. As a purpose of this project, the state of the art bidirectional encoder represents from transformers model was used for this NLP application. An NLP pipeline was developed to extract drug product information, ADME information from drug labeling with minimal human intervention. A paper on this automatic research has been published.

So wrap up my presentation, I would like to stress AI technologist bring opportunities to advance development and regulatory assessment of a generic drug. And we also need your input and insight on how to take full advantage of this opportunity to facilitate generic drug development. So please join the following panel discussion to share your thoughts and ideas. With that, I conclude my presentation. Thank you!

>> Hello, everybody! Good morning, good afternoon, and good evening. I'm group head formulation development from NOVARTIS, development center. Welcome to my talk on digital twins powered by machine learning and realtime insights by pharmacology R & D manufacturing.

Here is today's agenda. We'll discuss a little bit about the digital twin overview, machine learning based digital twins to additional topics of interest with some key takeaways from this talk. Let's get started. We stand on the brink of a technological evolution that will fundamentally alter the way we live, work, and relate to one another. In the scope and complexity, the rate of which this transformation is happening is unlike anything mankind has experienced before. The first industrial revolution which used water and steam to mechanize production, the second using electric power and the third used automation and information technology to automate production and now, the fourth revolution, which is building on top of the

third as the digital revolution which began since the middle of the last century also known as industry 4.0 and specific to the PhRMA 4.0. It's characterized by the infusion of technology that is blurring the lines between the physical, digital and biological spears. In today's concept, I'm going to talk about digital twin technology powered by machine learning which keeps us at the pace of industry 4.0.

So what is a digital twin? A digital twin is a virtual representation of a physical process to understand the physical counter parts characteristics. It can be used before performing the actual experiences or investment in the physical aspects but incorporating multi physics simulations, data analytics, machine learning and artificial intelligence capabilities, digital twins will be able to predict the impact of various parameters on the product performance.

When it comes to the digital twins in PhRMA, there's a lot of unit that happen sequentially starting from the raw materials, excipients and PAT to the final product of the finished dosage from the injectables, oral dosages and suspension, liquid suspension so on and so forth. So depending on the type of complexity involved, these digital twins can be characterized as simple, computational, machine learning digital twins or even machine twins if they are also integrated with tools for some realtime concise.

Committed to the process, digital twins in PhRMA, I have listed a few examples of the processes where digital twins can be made including homogeneity, so on and so forth. So if we consider the process of the digital twin as a black box, the various inputs is material properties including CMAs, including CPP, equipment characteristics, et cetera. And impact with all of these parameters, on the product quality. So if you're wondering why we need these digital twins, according to the US FDA guidelines, the element of risk is important during the filing of the manufacturing process. And this, during the process development and pharmaceutical manufacturing is essential in order to understand without the need of heavily reliance on physical, which is highly prohibited of the manufacturing scale where we usually target best in quality. Here I have given the example of the auto blending process where the inputs and be outputs are showcased. The inputs being made where the properties are included these flow characteristics -- and all of the outputs being blend uniformity and characteristics.

On similar lines, this is how the inputs and outputs for the digital twin look like. Again, here, the inputs and the outputs for this correlation of the digital twin where the inputs are particle size, deposited, the material, process conditions, including meeting time, speed, et cetera and outputs being granular size distribution, presentation, which in turn decide the drug release rate, tablet hardness, et cetera.

Here you can see an example of a simple digital twin or complex digital twin. What are the different measures that will decide whether the digital twin is a simple digital twin or a complex digital twin or where the blending is as an example. Again, here on this slide with blending as an example, the architecture used in leveraging blending digital twin for needs in blending is showcased so these are the inputs at different scales including equipment characteristics, process conditions, individual characterization and depending on the simple digital twin, complex digital twin or machine learning digital twin, the level of insights provided for decision making will be different.

Coming to the machine learning based digital twins, the talk of today's talk. Leveraging data based, capabilities is a growing area of interest with great potential of providing realtime insights and process development cycle. Conventionally, in processing this, simulations are used to obtain sites without having to do the actual experiments which are highly expensive and time consuming.

However, there are scenarios where even simulations are treated, as time consuming because these are heavily computationally intensive and also would need expert users to move the simulations and this would often hamper the use of C of D, PBM or DEM by the pharmaceutical scientists. In these scenarios, these machine learning models can be applied on simulation data or existing historical data to provide the practitioner on the fly detail level insights obtained from the simulation as well as these can be used with process understanding and realtime decision making.

There are few case studies where we have tested these machine learning models and one case study I have brought to demonstrate today is on the angle of repose where this is used from 53 simulations and the machine learning was developed. This is to predict the output without having to do the actual simulation. Here is a snapshot of the data using this machine

developed model. And here's a list of the top algorithms used for supervised learning. In this case, linear regression did not seem to capture the underlying physics well. And we had to try some additional algorithms. This represents the data very well. This shows that an initial investment in simulation helps to build a powerful model with good predictive capability for providing realtime insights to the practitioner and eliminated need for future simulations within the parametric space where the simulations were already performed. With that, I will now be moving to additional areas of interest drawing light on the futuristic areas where we need to invest more time in the pharmaceutical sector.

One emerging area is physics informed neural networks. Before talking about that, I want to draw your attention to the complex processes in had pharmaceutical development. Let's say, granular, which is highly complex and non linear in nature, making it difficult to capture all of the phenomenon, to extract the data.

In such kind of conflict, processes, there is a needs to integrate the loss of physics as well data driven models, for more accurate -- in them. This is further used to identify process characteristics which can predict the use of, let's say, the example of granular, reducing the manufacturing cost.

One other potential application is the ability to identify patterns or trends in data from existing data pools and predict the study axis while providing insights in the combination of the right choice of excipients, composition, formulation, the technology that will improve the probability of success in these studies so on and so forth. So this we believe is one potential application of AI/ML algorithms to help identify the patterns in historical data.

With that, coming to my concluding remarks. Machine learning based digital twins once developed can provide on the fly and in- depth insights which can be easily deployed by pharmaceutical scientists and are also heavily computationally intensive like the conventional simulations after an initial investment of some time and efforts. The potential of machine learning can be utilized in minimizing the study burden on complex development programs and also in minimizing the number of experiments, cost of development and accelerating the product development time lines.

Digital twins powered by machine learning can be deployed

by realtime insights in pharmaceutical R & D and manufacturing and digital twins powered by PINNN is an emerging area that excels our predictions made by data driven networks and it was great potential for modeling complex processes. AI/ML algorithms can be used to identify trends, patterns, in data and predict the studies by providing insights on the combination of the right choice of recipients, composition, formulation, technology and et cetera. That will improve the probability of success in BE studies. With this, we would request FDA to invest time in these futuristic approaches and provide support in establishing the framework for including insights from data driven technologies and regulatory submissions. Thank you!

>> Moderator: I would like to thank both speakers for the excellent presentation and I would like to welcome other panelist to on your camera.

Here's a list of our panelist. We will spend twenty minutes on the two panel questions and in the last ten minutes, we'll try to accommodate questions from our audience. With that, I would like to start our first question. Okay. I see a quick question from who has a little technical support to enable her camera. Let's start our first question. So the two presentations discuss the use of AI to help the review process as well as manufacturing process. I would like to hear from the panel members on your thoughts in terms of using AI for drug development. And also comment using the public data of the reference listed draft to create AI tools. That can facilitate the generic drug development and assessment focusing on any specific needs. I would like to start from Laura.

>> Laura: For my comments I thought I would focus on a different use of AI machine learning. Whatever you would like to call it. I saw discussion in the chat box, computational approaches. And what I am mostly interested in is how we can use these approaches to accelerate generic drug repurposes. So by this, I mean finding new uses of existing generic drugs which is a way to get new and affordable treatments to patients faster. This approach can save our healthcare system billions of dollars each year and we saw through COVID, how this can really be a game changing strategy. So the challenge where we need these computational approaches, AI and machine learning is there's so many data on generic drugs that have been studied for decades. It's difficult to know which repurposes opportunities are most worth pursuing.

So AI/ML approach can be use to quickly analyze vast

amounts of data on generic drugs and my non profit reboot RX made some exciting progress using machine learning to sift through thousands of published studies of generics in weeks instead of what would typically take years. This has enabled us to identify the most promising, non cancer drugs to repurpose for cancer treatment and quickly generate data packages on these drugs. Now, what we see as an opportunity to extend this work, to integrate additional data types like molecular data and real world data, and create a data and analytics platform that can be used across the industry really, for customized analysis for drug repurposing.

We think this ML powered platform would really transform generic drug R & D by doing two things. One, accelerating the pace of scientific discovery and two, specifically de risking the process of prioritizing drugs for clinical trials. So these are the comments I wanted to share, thank you very much for the opportunity.

>> Moderator: Thank you, Laura! Any other panel members would like to jump in and share your thoughts?

>> Ravi: This is a wonderful presentation to talk about the use of AI process and realtime insights and R & D manufacturing so it's an honor to be a panelist today and I would like to take a stab at the question where we are talking about potential use of AI in other areas of drug development. Generic must be bio equivalent to gain approval but there's stances where they are not sufficient. And that the path to approval provides strong studies. Thee can be difficult and require significant number of patients that will take many years to approve. So in such instances, tapping into the real world data, using advance analytics and AI perhaps, there's a hybrid to have smaller clinical trials may be an area to look into. Having said that, the application, we all know, in the development process is relatively new and there's certainly a progress that needs to be made in developing scientific robust methodologies, algorithms and predictive cost models to enable decision making.

While the FDA released multiple draft guidances to enable the use of RWE for regulatory visits, for specialty drugs, there's no guidance documents under development that can in fact, have a generic manufacturers so investment and prioritization by the agency in two areas, one, around developing guidance documents and two, around advancing the development of robust methodologies to enable the use of these

techniques for regulatory approval. Just know our mission is to be a global leader in generics and bio pharmaceuticals in improving the lives of patients.

So we also welcome any opportunity to collaborate with pilot products with the agency in advancing the science and application of this techniques in the generic drug development process and bring generics sooner to those in need. So with that, let me pause with my comments and go to the next.

>> Moderator: Thank you! I appreciate that. Now, I'm going it turn it over to Sunny.

>> Sunny: Thank you for having me as panelist here. I would like to start with the shortage of the modeler and the FDA's resource constrained. When I hired new employees, almost everybody comes with machine learning background. So given the shortage of the modeler, I would like to make cooking as an analogy. I would say the PK modeler is a skilled chef in the FDA reviewers and adjudicators and I would like to say machine learning is more like, a prep cook where we can hire virtually unlimited number of prep cooks. So this prep cooks can dice onions or whatever, to streamline things. And the chefs can have everything already prepped and then shorten the cooking time and developing recipes and also, this prep cooks can do certain things so that the adjudicators can shorten their time line and reduce resources.

So for example, it's increasing the rate of FDA first cycle approvals from its current baseline level which is around the 20% according to some publications to a high of 66% that could reduce the time to market to the generic drug development by around 13 months. 45 percent resulting in 3.5 million dollars declined in the capital cost to the generic applicant across all types of A and Ds. So appointing to 2019 study by the GAO, major resubmissions for A and Ds were application insufficiency and deficiencies in this drug quality and the application priority status. So if we could develop the AI tools to streamline just a checking in basically making things like, it doesn't have to go to the FDA reviewers. This too can be available and the sponsors will be able to check whether they have sufficient applications in the first place and this type of prep cooks can reduce an enormous time or effort in general.

>> Moderator: Thank you! I really appreciate your nice comparison, the last explanation of the whole thing. I appreciate that. So any other questions for this question? Sound like I made our panel members think really hard now. We

can certainly come back to this question because it's a big large question talking about the new areas and any particular future direction where we should work together and invest. So question number two goes to the adverse reporting. So talk about the opportunities and challenges of integrating data from the post marketing adverse reporting with other data from the public generate a better understanding, for the selection, evaluation and approval process related to the AEs, adverse events and this time, I'm going to start from Dr. Mark.

>> Mark: Thanks, my question is -- hang on a second. My question is if we can extend it to what we do with pharmacology and link these inputs into the various things that describe both the recipients as well as the profile of absorption and bioequivalence criteria and to link them ultimately to large data bases of adverse events, perhaps, internally from the agency or perhaps medicaid, Medicare and the approaches that epidemiology uses and extend the farm Coe epidemiology into rather than just discussing the effects of drugs and drug utilization on outcomes and large populations but also, excipients and other things described by these methods to outcomes using large data sets. Again, like, medicaid, Medicare, internal FDA data bases.

It occurs to me, there's a lot of significant challenges to this. There's always challenges in making large data bases both practical, logistical, scientific as well a statistical. So I'm wondering if this is something that can even be considered. Is it feasible? Any way? I see it initially as, to some extent, a validation of our whole paradigm in what bioequivalence means. Does it ultimately predict, correlate, or tell us anything about the patient's outcomes? Is.

>> Moderator: Yes, thank you, Mark! I think you nicely elaborated the cross talk, across different data from different methods about equivalence and excipients and formulation design and mechanistic understanding of the exposure response. If we can put all of this data together, hopefully, the system will allow us to predict the clinical performance of the intended product. Thank you, Mark!

Also, I would like to hear Dr. Bing, can we hear your thoughts on this question?

>> Dr. Ping: First of all --

>> Moderator: I also hear a lot of background noise from your

end. Now it's good.

>> Dr. Ping: Yes, thank you, Lucy. I think today we're actually talking about forward thinking topic for especially, for generic drug development and also the regulatory science for generic drug evaluation. And this morning, we also heard industry speakers, recommendations and their interests in exploring this interesting area. Talking about the post marketing adverse event report, as many of us know, that one of the main systems that FDA utilizes for post marketing research, is the FDA's adverse event reporting system. It is voluntary post marketing safety data base allowing the general public to search for information related to adverse event of a particular drug by reported by consumers and the advantage of this data base for AI and machine learning application is it is a web based system. It's publicly available. A huge amount of data can be collected so providing a good opportunity for potential AI and machine learning application.

On the other hand, we heard specially, you know, from a presentation that a machine learning model needs high quality, accurate data in addition to large quantity data to train and develop machine learning. So we know that our data base has some limitations. For example, since this is volunteer based data input, and also publicly open, we see duplicated reports. We see incomplete reports, unstructured data and also information in this data base and this report, it reflects the reporter's opinions and the observations. So validation of the data may be a challenge for the AI application. But none the less, our current way which is using a very traditional way which is high in our human brain to sort of sort such data trying find the safety signal and the association of a particular drug is a huge challenge. I consider that, you know, the potential application of AI and machine learning can help and promote data driven decision making process.

And also, as an extension, also you know, to sort of touch upon the first question, I think AI and machine learning also has the potential to leverage other data base sources such as, you know, met line. Some popular literature data base, even that our FDA's voiced review report, you know, sort of to extract the data and provide information that facilitates our scientific and also, regulatory decision. And as was mentioned in his opening remark, we're thinking about for the next five years, maybe, you know, for the next ten years at GIC, the potential to utilize this tool in pharmaceutical development as we start opening our mind and exploring this area.

Actually, to think about it this way. FDA itself holds an oath, a big data base. The application submitted as well as the evaluation report, evaluated by our scientists, right? And thinking more, you know, from the global point of view. There's a huge amount of data from various areas of regulatory agencies that could be leveraged using AI machine learning technology. So I'm glad to see that we're starting to think about this in the generic arena. Yes, thank you!

>> Moderator: Thank you for your insightful comment comments. I just want to follow up with what was mentioned on question number two. Like, how we can use AI to help us do some prospective, post marketing surveillance and as we kind of heard just now, we want to cross talk across different data base and really, use those data base to use machine learning to identify different signals. I guess really to boil down the question, it's mechanistic. If API related it can be tied to your assessment but if it's formulation is, if it's excipient related, it goes down to how much you understand that excipient, so I think a lot of understanding of further development is needed. So Meng, I see you raise your hand. Now I will give it to you.

>> Meng: Actually, FDA in the past years, they have invested a lot of resource to conduct the post surveillance. This rights. If we get a high quality of data, the insurance data, claim data, the health record, they will be more, you know, specific, more details regarding the patient, the characters and also, the description of the AE. But if we're talking about the public data, I think, Bing already touched upon that data. The other side I could think of, it's social media or some data discussion from the forum because I see in the past years, some research has been carried out starting from the academia. They are using, AI, machine learning, the related technique to screening all of the social media or some of the forum.

I can see an example studied. They just studied a patient for a particular area, the patient will talk about this and discuss all of the drug use or all of the, you know, adverse event. And then they study, just study, just with them, all of the discussions from the following and they extract some information from there. There could be another direction to use public data to study the AE related information. However, I think, as I mentioned, data quality is still a key for the model, whatever model. Not only machine learning model. Even for some traditional model, data is the key. So how to

generate an affordable, high quality data is still a challenge from the data for the public resource. That's my comment, thank you!

>> Moderator. Thank you, Meng. Now we'll come to the next speaker. I see your hand.

>> Thank you, Lucy. I can't agree more with Mark and also, who have already spoken on this topic. I would like to reemphasize that data mining, drug safety report data bases, especially the medical literature and other digital sources, can play a deep role in implementing the information about these adverse events, during clinical trials or post marketing surveillance or any other sources. Data mining for these purposes also provides an early warning system and can help us understand if there are any engages with respect to the new association among drugs or if there are any risk factors associated with the introduction of any excipients or any other drug interactions found. I would say, this is a very important area we need to invest a lot of time on, as well as industries and also, to improve the way we collect the data from these, you know, these various digital resources. There's a lot of data available but then, like, Meng already mentioned and I think, Bing also mentioned at this point, what is really important here is which data we are using, how we're trying to segregate the data, to train the models that we have been developing and for using them to predict. So this really plays a crucial role. I think we will need even more deeper layered. We need human kind of intelligence, not just the machine kind of intelligence where some kind of linear or non linear model is derived and we're trying to predict it. It requires a lot of intelligence and this is where this goes for the substance of this kind of AI/ML modeling. So I think we need to invest segregating the data and getting diverse data. We don't want to make it just on one particular set of data which is not representing a big data pool and then, you know, we would try to predict and not represent the realtime, real world scenario.

This is one loophole here. We need to be very cautious about it and data we feed in the model is to show the success of the prediction so we need to be very cautious about this. Thank you!

>> Moderator: Thank you! Cindy, I saw you raise your hand right now.

>> Sunny: So there's a couple of points. First that the

evaluation of 50 metrics predicted using public data and known adverse events from compound as well as administration, is very practical and one of the less complex problems. Secondly, constructed models can parse it from a risk evaluation and mitigation strategy, for A and D submissions. That are submitted for the same RLD. This would also help understand and rank the fidelity faithfulness of the risk evaluation of the generic submissions compared with those reported for the RLD in clinical trials that GOV. Net watch, et cetera, as well as the comparability between the risk evaluation of ANDAs for the same generics.

>> Moderator: Thank you, Sunny. I appreciate your insights from you all. Before we close, there's two things I want to ask. First, I want to go back to Ravi, you shared there's going to be an initiative on this. Out of my personal and curiosity, do you mind to elaborate a little more, provide a little bit more details? So the question is on the transparency models and the question is about the black box term. Sometimes, we in AI and machine learning, we see all of these things. Is it actually correct? Because we actually don't have this question explicitly available but there's maybe other situations and the term black box is used to describe models where the developers may purposefully don't want to share their details of the model. So I guess, the question is to you all, I mean, how can we really interpret the term Black box and how can we, in a community, how we can avoid the second situation in second situations. Also, I want to look at this.

>> Sunny: I think the very first, there are models behind the scene. It doesn't -- black box doesn't mean there's no models. Models behind the scenes. Here's the more important thing that is that we need to establish the validation part. Whatever models we use for certain purposes. For certain questions to answer, then that part is probably more important than whether it's black box or gray box or whatever terminology we use.

>> Moderator: Excellent, Sunny. I really like that response. So hopefully, we have addressed your question. Any other feedback on this?

>> Meng: May I? I just want to add a little bit about model transparency. I think, as Sunny mentioned, black box is not really black. I think theoretically, when they call it not

analytically closed. Meaning, there's no analytical form to describe the process. I think, it's, first of all, no method is perfect. That's the beauty of the model because we don't need to know the close form regarding some unknown process. But at the same time, I think, if we call it shortcoming, has there been a lot of effort that has been made to mitigate the shortcoming? Like, many scientists working on so call, variable importance algorithm to identify which variable is more important given the model?

And another thing actually, I want to talk with transparency is reproducibility. It's that we, if we let's say, if we propose a model I think, the reproducibility is at least equally important to the transparency. That's it. Thank you!

>> Moderator: Thank you, Meng. So Ravi, we have one minute.

>> Ravi: I want to take a stab of your question. So I think the power of the R & D, the real world data, lies in our ability to tap into enormous amount of data providing highest statistical power, right? So R & D including EHR has a huge amount of data on patient outcomes and diagnostics, lab tests, prescribing patterns among others, science of emerging data so as long as the AI methodological standards are robust enough and if the data source is fit for purpose, then the evidence may be potentially used to support regulatory submissions. What I meant is there's a gap there, where there's no clear guidance and any efforts to provide those, develop those guidance documents and also, improve the science and methodology would be welcomed. And being one of the leaders in the generic space, we offer the opportunity. It's new. There's images that just begin to form shape but there, the opportunities between us and the agency and resource will help us identify these methodologies. We're not there yet but that's the way we should go forward. I hope that answers. There's an opportunity because the data infrastructure is changing and the technological -- landscape and the computing power and all of these things that were mentioned, also are improving so we just need to make sure that we have the right way to take advantage of the opportunities that may present itself.

>> Moderator: Thank you so much! With that, we have to close this session. We have run over a couple of minutes and I want to thank the speakers and panel members for your contribution

to this session. And also, the audience for your time and patience with us. Now, we're going to take a quick lunch break. Thank you all!

>> Maria: Wow! What an amazing morning of presentations and panel. Thank you to our faculty and we greatly appreciate your participation. As a reminder to all of our participants, if you have any questions, please remember to enter those into the Q & A box and indicate who the question is for. As she stated, we're going to return promptly at 1 p.m. eastern time in the United States. Thank you and we look forward to having you back for this afternoon's session. Have a good lunch, everybody!

>> Sarah: Welcome back, everybody! My name is Sarah and our next session is session 3 which will be public comments. So we'll have two different parts to this session. We'll start out with five short comments. And then we'll go to a listening panel. So throughout this session, we'll have a panel of FDA participants that will be listening to the comments in the prepared presentation and then in the open mic session which will be the second half of the session. I just wanted to start by introducing our panelist, we have Rachel Rob. I would welcome all of the panelist I just announced to make sure you have your camera on for the duration of this session. Now I have introduced our panel. I'm going to introduce our next speaker. So they will have five minute presentations. We'll start with Raja who will be talking about a need for bio relevant, bio predictive in vitro for LI, complex generic drug products. Next, we'll have Valerie, Ph.D., the senior director and project lead, global medical affairs and at Teva. We'll be discussing the remediation of this. Next, we'll have principle and managing partner at RAAHA, LLC and we'll talk about the endogenous nitro SAGS. Our fourth speaker is Janet who is the VP of North America, generics regulatory affairs at TABA and will talk about green propel ENTs and our next speaker is the senior VP. Who will talk about the expectations, expanding the span and aligning our partners. Let's get started.

>> Good morning, everyone! Thank you, Sarah for the kind introduction. I want to make a public comment on the need for continued research on bio relevant and buy row predictive in vitro release methodologies of long acting inhalation and other methodologies. This is from working with many colleagues from

the industry, communities as well as the PKPD software vendors.

Let me start with a disclaimer. These opinions are expressed herein mine. I do not reflect other members of the trade organization. My sincere thanks to all of the colleagues who helped me put this comment together. Mainly the SANDOZ clinical development and the staff for the association of accessible medicines and also FDA Generic drug science and research staff who provided me guidance during this process.

I would briefly describe the role of bio relevant and bio predictive methods in vitro methods of generic drug development. I will identify the areas of need. We have achieved a significant progress in the last five years in developing mechanistic modeling tools for the performance. However, modeling has -- lack of bio predictive methods to generate such data is limiting the availability of the mechanistic modeling, productive development. These direct companies do not have the capacity to develop the individual tools from scratch for each technology platform. So there is a need to develop basic in vitro methodology for complex technology platform products and there would be a huge positive impact of the research in developing in vitro methods to predict in vivo outcomes on the acceleration of the drug development while reducing the clinical cost. The need for bio equivalent in vitro area, we have three areas to focus. For long acting injectables. The challenge we face is the short duration of the test that leads to poor prediction of the long in vivo release. The opportunity to develop methods that provides useful input data for mechanistic modeling. In this area, our challenge is to develop the in vitro method physiologically relevant, discriminatory. Inter lab transferable and in the process. In this inhalation drug product, we can see this is using the next generation but not reflecting the studies. Also, it is useful to develop methods that predict in vivo absorption from different regions. Our request to the FDA is to continue the GDUFA research in developing these methods. The method of focus of research in our view are, the dissolution methods that predict the in vivo performance of longer acting injectables with a one to six month duration for dosing schedule. The second that matters, that are used smaller dissolution area and commercial equipment. Methods have to be product and technology specific suitable for long acting injectables, with the acceptable variability. The third is to develop methods that predict the in vivo performance of the DPI and MDI in the inhalation area. In addition, we request OGD to continue to publish the outcomes of their research in scientific journals, post them on the FDA

website and share them with the FDA with meetings such as at this. We highly appreciate the OGD for providing us with this opportunity to speak up and we hope that our recommendations will be considered and implemented as resources are permitted in the next five years. Thank you!

>> Next presentation. Good morning, good afternoon, as they have started to test the product, we start looking at the API related nitrosamines and we can see this is the main challenge of this. My presentation is focused on this complex formulation drug product manufacturing. So what is our option to immediate this in drug product? We have mainly three options presented here going from the lower time and cost consuming to the higher time in cost consuming.

The first option is to set an appropriate acceptable intake with the alignment based on scientific purpose, this is the simplest or fastest option to be compliant. The second option is to reduce the risk of using low nitride. In the present, we are looking at the high load that will obviously have the highest impact as they contain a nitrate. We will come back to this option in a specific slide. The third option is a formation of the product to avoid use of identified -- entity, a work on the manufacturing process. We will discuss further in the last slide. So why is it not preferable? So the formulation is time consuming since we need a new development with several PKs, manufacturing of batches, six months stability and submission. Roughly, it takes a few years until the product will be marketed again. This activity has also an important cost and will impact the development capacity of the companies, therefore, profitability of the product will need to be evaluated if the formulation pass has to be initiated. So what are our limitations for setting an acceptable intake? Acceptable intake is based on the surrogate or in vivo or in vivo studies and sometimes based on the availability. The challenge here is that there is no clear guidance on how to do a read across but also how to have the complex nitrosamines. So if the tool is not found, it's urgent to find new tools and support new research to guide the industry. The risk benefit to patient this impossibility impacts the new launch of product but also, impacts the development of new product due to the testing burden in developing this complex and analytical. No remediation work can be because of the uncertainty of the limit. So recommend to set interim limits based on the actual data availability and ICH M7 principles until further guidance is available.

For the excipient role on this, there's a recent initiative from LHASAA to initiate and collect nitrates analytical results from the industry. Main excipients suppliers aware of the need to reduce levels of nitrates, but not necessarily ready to remediate, sometimes because of large No, ma'am and investment needed and sometimes because PhRMA industry is the no the main market. We need to help the supplier to limit it. Some suppliers started to remediate but the availability of these rates will take time and con sequentially possibility to remediate the drug product is delayed. Sometimes the source of nitrate is related to the excipient. Some of the suppliers refuse to have a limit of nitrate the in their COA meaning it is going to be challenging to put in place a controlled strategy in the finished product.

So the question here is how to do this within the finished product if excipient supplier is not ready. There's several aspects to consider for remediation, for the formulation. We are only in the beginning of the research. First, API. The industry has to better understand the impact of the physical properties of the API. For example, the crystal of the API or impact on this formation, during finished product manufacturing. Parameters of the finished product manufacturing may need to be better understood such wet process, temperature of drying, loss of drying or PH. Can we use scavengers? We also limited by the level in the quantities to be used to see the effect. In general, the solid solid reaction has to be better understood if it is from the kinetic or the para meters of the API. It looks like that at this level, the formulation is applicable to new product development but not for commercial product. Thank you for your attention.

>> Thank you for the kind introduction. I'm going to talk about understanding the impact of endogenous VER nitrosamines. What I have to say is on behalf of the generic industry. We all know the innovators and over- the- counter have been profoundly impacted by the detection of nitrosamines in several drug products. The results of these findings have led to an unprecedented burden on the group, confirmatory testing and sometimes attempts to reformulate.

Now, nitrosamines are possible and carcinogens and a concern so it's quite justify we should be cognizant of their presence in drugs and try to control them at the lowest possible level. However, we should not lose site of the reality that the sources of nitrosamines can be exogenous

studies as early as 196 shows that nitrosamines can be generated endogenously with simultaneous creating of nitrate and remains of animals. We excrete them in our urine every day. A clear evidence of endogenous. The evidence of this goes on and on. We have also seen that drugs like this listed here. In fact, they have seen that 45 to 75 percent of exposure to nitrosamines is due to endogenous. This is tough to study because nitrosamines degrade in our body quickly after activation by alpha hydroxylate to form products. The bigger the nitrosamines, the more complex. Also, there's about 300 FDA approved and secondary and tertiary drugs that have this, to form an this. Yes, it can be forming quite rapidly. So before we become ultraconservative and sometimes, unachievable limits to this, we need to understand if they are formed endogenously. Imagine if even 0.1 percent of a drug under goes this in GI tract, the risk related being controlled at a few PBB in the drug would not be relevant. Some of you may be wondering as to why I'm talking about this specifically in a generic forum. That is because generic industry has a unique situation where each of the drugs we have talked about may have several parts to them and thus, the sponsors trying to do these studies would cause redundancy, confusion and even contradictory outcomes.

Also, generic represents 90 percent of all prescriptions dispensed in the U.S., thus, it would be greatly beneficiary if OGD spear heads these studies and invests some of their resources in studying endogenous. If we are chasing with this IM image to visualize, I conclude my talk, thank you very much and have a great day!

>> Janet: Pharmaceutical aerosol, as far as pro Pell LANTs. Historically, CFCs are used but they reduced layer. With the Montreal protocol, this is an international treaty adopted in Montreal in 1989 and was created to restore the ozone layer. The protocol was made defective January 1st, 1989 and has under gone 9 revisions or amendments since then. The most recent amendment to the Montreal protocol was on October 15, 2016. With the United States leadership, they are phasing down HFCs which is known as the KIGALI amendment. Now, why phase down HFCs? They do not deplete the ozone layer but are powerful greenhouse gases that contribute to climate change. How will they be phased down? Well, they will cut the production and consumption by more than 80 percent over the next thirty years. Developed countries will reduce HFC consumption beginning in 2019 and most developing countries will freeze conception in

2024 but there are a small number of developing countries with unique circumstances that freezing -- that they will freeze consumption in 2018.

In April of 2021, they pledged to ratify the amendment. These are some that are widely used in the industry. They already have gas quotas from 2022. We're looking at 85 percent reduction over the next 15 years. The cost of current propellants. -- to reduce the carbon footprint. Several companies have announced that are strategy with a 2025 target to switch to a green propellant. Here are some examples of some innovative companies that have announced that are strategies and planning for implementing green propellants. Generic companies need to respond. Respiratory drugs are finally seeing generic competition but many remain not generic. Switching to alternative propellants they cause delays and transition would require significant time and cost and could potentially result in the withdrawal of developed generic applications. In the main impact will be on patients who depend on cheaper generic drugs. The health of patients and the health of the environment must be a focal point. Synergy the tool requires a well thought plan and support. Of course, the generic industry with the benefits they bring to the environment, however, the potential impact on the product line cannot be ignored and researched into the new propellants on the potential impact of respiratory drugs would help assist the health authorities and manufacturers. So here is a three part proposal. One, perform early development phase investigation to determine any incompatibility between current products and future green propellants.

Two, generate early stage performance data to determine any impact on the performance. And three, make accessible a single DMF of non clinical and CLINal safety studies for new clinical propellants. This helps with the transition of the pharmaceutical industry to these novel propellants and review any potential duplication of animal or human safety studies. Thank you for your time.

>> Greetings, everyone. The theme of my topic is expectations from GDUFA #, expanding the span and aligning the partners. The disclaimer: We have all witnessed the successful journey. I would like to talking about the scientific enhance wants fixing some of the common problems with culture by industry. With any application, the point is with respect to this. Who needs -- permission from this has dispensed. Similarly, there are several departments --

Lead times with all of these variants, they have now doubled or tripled and are not guaranteed. The drug shortages lead advance planning in the supply chain with all associated items. Initial review and life cycle management. The agency is making good progress in technology. They hold a lot of advancement. Dash boards and -- this is helping the advancement of all of these, that are acknowledged and appreciated. The tracking will -- and (inaudible).

With restricted access, they are not able to -- we wish to solve these disciplines and hence further coming communications. This will benefit a large amount of planning. Coming to the DMF. Time can be saved starting with the evaluation is a part of the comprehensive assessment and guidance -- to fight the applicable -- (inaudible). This will be supporting if the agency takes the lead. Communication challenges with agency is always for any form. Case of this -- this will be -- in terms of the technologies and maintenance of aging facilities. This is the right time to have changes to the guidance. Yesterday, change of this -- is -- even after this is advocating for emerging technologies and a lot of advancements are happening in manufacturing the space. Like wise, change in the filtration is vice versa, determined as this. This will also help in the building aging facilities. Scientific enhancement.

This will help firms have a higher quality of submissions. In this guidance, in line with the current thinking citations as most of them are several years old. Meetings, it will be accommodating if the agency allocated three meetings for all of these forms. One for the facilities, one for the status on filing and the quality and other associated permissions and the last one, on the scientific advice on technical advancements. Conclusion, there's a few other which we rarely approached. Requesting them to expand the span -- shorter time reviews and action. Acknowledgments, we're thankful to the agency for the opportunity provided. Mansion and colleagues for this support. With this T I conclude my presentation, thank you!

>> Moderator: Thank you to all of our speakers for your -- there we go, okay, that's for later. So I would like to thank all of our speakers for their thoughtfully prepared comments and then, I want to start by asking our panelist if they have any questions, any clarifying questions for our speakers. This sounds like everyone is clear. If there's no clarifying questions, if any audience members or attendees have a comment they would like to share, please use the raised hand function.

We will call on you and unmute your mics so you can share your comment to the panel and to the group. And you can also take advantage of the question and answer box if you don't want to speak to the group. If you would rather type. So if you have any comments, please use the raise hand function in Zoom and we can call on you so you can share your comments.

>> Raja: I just want to start the conversation. So from the morning speakers, from the morning speakers and the speakers that initiated the conversation on the next five years. All in one aspect, was the in vitro put money into the mutual research in identifying the in vitro models for similarity. That's my comment here. Just basically asking to set aside money to continue research, broken down by we need more specific research in the areas of LA, LAIs and also inhalation and ophthalmics so that's where the in vitro methodology is becoming more like, separation from the quality aspect. So the quality method that is from in vitro predictive methodologies. So that may be an area, like, what do you think? Are you feeling that the QC methods and then also the in vivo development methods are going to be tough? Because the agency has to approve two methods here. It's to have two methods, one for QC and one for predicting the in vivo. Do we see this as something that can be self- supported? Maybe for Robert? Knowing the direction that it's heading, do you see an area that can be entertained?

>> Rob: So the point is to hear people's input so we can't give you an answer whether we support it or not but it's to gather the input from stakeholders to say, why should we invest in this versus another aspect. So thoughts about what number of products are effective and also, from your perspective of industry, right, what would be the value of this versus other aspects, right? Do you think it's more important to spend resources on complex generics versus, you know, making the tablets and capsules about development faster? Those are trade offs. Input from the industry side would be helpful.

>> Sarah: We have a raised hand in a panelist group. Would you like to make your comment?

>> Leslie: Thank you, Sarah. I didn't know whether to bring it up or not but since no one is making comments. Sam just called me and said, I should bring it up because I brought it up during our discussion. And it's not necessarily something that the generic industry is going to like. I am concerned and I think a topic not necessarily here but in the future, I think

we seriously need to go back and talk about using C max as a measure of rate of availability. There is no doubt that when C max significantly changes, the rate has changed. And yet we do agree to do this. Now in some complex processes, we will allow area under the curve up to two maxes being the comparison. But that is sort of a statistical test that the agency has developed in terms of how you do that.

I think from a science perspective, the statistical test is not how we should be doing this but we should be talking about how relevant C max versus area under the curve up to T max is. And I think that has not been addressed to a significant extent in the past and is an area that the agency should address in the future. So I don't really think that you want to discuss it here in this, but I'm going to, I'm going to write an editorial for it on the topic. And we'll see how it is addressed in the future.

>> Rob: We look forward to your thoughts on that. For many years, our regulations say the rate and we said that, what we'll do is C max so certainly, we'll look forward to hearing your thoughts on that.

>> Sarah: Any other clarifying questions from the panel? Great! Thank you. I think we have another raised hand.
>> Pannala: This is a follow up comment. I would like to thank FDA for giving me the opportunity to present today. In context to my presentation, a new drafted guidance has been introduced for further quality assessments which is one of the -- to -- on the approval. I think, FDA for giving guidance. Thank you!

>> Sarah: Okay, thank you! We have a few questions in the Q & A box but I wanted to clarify this session is more for public comments than public questions. So what we really want to do is hear from all of you with any comments you may have. So again, feel free to raise your hand or type any comments into the Q & A box. Any comments? I take your comments into consideration.

>> Maria: We have two people. Please unmute them.

>> Hi, everyone! Thank you, thank you very much for the sessions and discussions. It's really nice and really open windows for many things to talk about in the future. Especially for us as generic companies. My question is always

is that I have a concern. If I prepared mine with the guidance of the FDA and I'm really abiding by all of this, once I go to the Middle East or Europe or any other country, I will face a problem that my -- will not be accepted or I have different guidelines and different approaches and so how can really, have a harmonization but really, saying I don't need to repeat either of these studies, as you know, the bio equivalent or for example, that we need for a different ethnicity or something like this. We need to repeat, like -- this is really a cost for the generics and it's a tool that suffers delays in the release of a product. I'm just really, thinking loudly and I would really like to have some answers at least in this future to do. Thank you very much!

>> Sarah: Thank you. Is there any clarifying questions for the panel? We have another hand raised in the attendee list. Can IT unmute them?

>> Hello, I'm a micro biologist from the University of (inaudible) in Pakistan. This was a very wonderful program to update how -- registration and -- learning knowing drug development research, we developed a certain -- drugs in certain -- for this other. FDA concern is these areas -- in our educational community. We need to learn how to -- FDA and all -- with this we can -- in the future, we need to have many programs to the -- develop drugs in order to do this? (Inaudible) can you collaborate to the resources in our education commission of Pakistan to train the scientists to -- product registry for FDA approval?

>> Sarah: Okay, thank you! Do we have any additional comments?

>> Raja: Sarah, there was one question in the Q & A regarding the person who raised a question. They were asking whether she has a comment saying I think a broader approach would appear to be able to -- correlations, talking about the in vitro method and simplify them as one better way to understand the relevant parameters. So what she is suggesting is if you have a QC method and then also, in vivo method, relevant method, so one could actually develop some kind of a method that actually correlates with the in vivo and then later on, you can reduce the testing to meet -- the QC method type of thing. That's a good idea so one can start with actually with a complex method and then, e slowly by knowing what is relevant, you can tone it down to the QC method. Thank you!

>> Sarah: Thank you, I think a lot of questions in the Q & A box may be related to other talks later. Does anyone have any additional, any additional comments? Okay, I think we may be able to just move on to our next coffee break, Maria, do you have any other information that we need to share right now?

>> Maria: Not for now. Thank you, Sarah and thank you to our public commentators and panel. We greatly appreciate all of your input. We also want to know that we do have a public docket that is open until June 10th which we are requesting if you additional comments, please utilize that. Shortly once the break beginning, I'll share the information including the link in the chat box. So if you have additional comments use our public docket. Also, throughout the day, if you have questions for the speakers or panelist, we do have a Q & A box. For now, we'll take our first afternoon coffee break and emerge promptly at 2 p.m. eastern time in the U.S. we're looking forward to seeing you in session four. Sruthi Kausik.

>> Moderator: Welcome back and welcome to session four on excipient effects. The presentations and the panel discussion during this session are going to focus on a wide range of scientific issues impacting generic product development and assessment that are associated with characterizing excipients and impurities related to excipients. We have the deputy director, and Dr. Andre, in the office of life cycle drug products are the OPQ are going to start the session with a short presentation to give us context for this first session. And then we'll hear from grace, principle application scientist of LASA and Dr. Kausik, an associate principle scientist at Merck and finally, we'll have two talks by Dr. January, in the division of pharmaceutical analysis and OPQ and director Bob, toxicology review of OGD. I hope you enjoy the presentations and discussion, thank you!

>> Good afternoon. The theme of this discussion is to discuss future research represented to the challenges and considerations pertaining to the risk of excipients. As background, this slide shows a prevalent pathway that leads to the formation of such nitrosamines impurities due to these excipient contributions. These are generated are termed, nitrosamines drug substance impurities or NDSRIs. These constitute a different classroom than typical small molecule such as this and they have a structural similarity to the active ingredient.

The root cause of this is quite simple. APIs often contain secondary function group and these can react with residual nitrates often present in recipients during manufacturing of drug product and/or shelf life. In addition to this, if related secondary impurities are present at high levels, residual nitrates and excipients can also react with these to generate nitrosamines. For example, recent publications show the likely reason for the NOR MAGS of this, that arise from the impurity, a by- product of metaphor men synthesis which later in the drug product, when exposed to a drug source generates this.

We are looking forward to the public comments as we address future research needs in this complex area. Thank you!

>> Good afternoon! Welcome to the afternoon session. I'm the pharmacy director in the office of safety, evaluation, within the office of the generic drugs. My goal is to describe the future challenges and highlight the opportunities to inform the safety assessments. There is extensive published literature on nitrosamines. They need tight control, yet, the discovery or drug products highlighted there's many data gaps. The chemistry formation, the reactivity and stability and mechanism of action, of carcinogens are not fully understood. Safety assessment is complicated as there are many sources of it, including the formation endogenously and their presence in food, water and our environment. How do we consider all of these source of nitrosamines when assessing their risk of drug products? Importantly, this has posed a new challenge. Excipients in the formulation can give rise to these which are data poor. That means there's little no no compound safety information to assess the risk. Optimized testing conditions for hazardous identification and risk assessment is being investigated.

In the absence of empirical data, risk assessment is currently being done using structure based modeling, computational toxicology, and expert knowledge. However the models themselves are data poor. Therefore, empirical data is needed to build stronger models to facilitate safety assessment of nitrosamines, in particular, NDSRIs. To fill these data gaps, collaborative efforts are needed to have risk assessment and control for this to ensure safe, generic drugs for American patients. We hope you find this afternoon's presentations and discussions engaging. Thank you for your attention. This is

the list of speakers and panelists for today's subsist.

>> Thank you, everyone! I would like to talking about the pre competitive data showing initiative. During this presentation, I aim to introduce the initiative to talk about the steps taken to ensure the quality of data and share with you our initial findings we have from the data base. To introduce this data sharing initiative, I would like to share the basic principles. The aim is to generate and share core data on the levels of nitrates in common recipients. Last to facilitate it data sharing a consortium has been formed to give access to this data base on the shared data base. Data quality requirements have been defined and agreed by the consortium to ensure data base will contain robust quality data.

The data base aiming to increase the knowledge, scientific community on nitrate levels, safe time, avoid duplicate testing when possible, and provide supporting data for nitrosamines data. This shows since 2020. It currently contains data for 678 studies for 79 common recipients. The consortium meets to discuss the data base and make sure it meets predefined quality standards and the contribution to share expertise and challenge and work together to share it with the wider scientific community through presentations like this and also through publications. It is very important that the quality of data is maintained and guidance is put in place. Experts within the consortium developed criteria based on several factors including selectivity, repeatability and accuracy. Data can be generated using any analytical method as long as the validation criteria is met. There's a field in the data base where it's recorded. And another important principle is that the data is on excipients not the vendors or suppliers. Along with the nitrate levels of recipients, we collect information on the batch and supplier.

However, this information allows us to complete an internal blinding process. This blinding is an essential requirement for the data base to keep the information regarding the excipient supply confidential. This was a decision made by the consortium as the data is for scientific purposes and not for business interests. I can talk more about this in the demonstration of data base coming up.

In this short demonstration, I would like to show you the results of the excipient remark. Once you have logged into data base, you can search for it using the excipient name. The

data base is made up of three tables. The first being excipient which is where we are now, just showing the name and number. The recipient results which shows the detailed results we received from the member organizations. There's 130 results on this. Let's look at this table. On the left hand side, we have the excipient name information. The first field is the nitrate limit of quantification. We then have the nitrate result. We do collect information on the nitrate levels as well. We have a few fields for the high level methodology information including a link to the validation criteria used. We collect data on the date of the excipient manufacturer, the dates the test was run, and lastly, the supplier and batch codes. This code keeps the excipient information confidential but it allows us to see the three results from the same supplier.

The batch code keeps the information confidential but allows to see the record one is different than record two, but record two and three come from the same batch. Let's switch to the excipient summary table. This is only made for two records, the first for nitride and the second for nitrate. This takes 113 studies in the excipient results table we were looking at and summarizing them to a minimum, mean, maximum and median concentration in these studies. Finally, once you review finishing the data, it's exported in a report. Now back to the slides.

My last few slides show the initial findings of the data base. This analysis was formed in August of 2021 with a data set of over 400 results of 71 excipients. This shows the distribution of results. Each of the colors represent the maximum, mean, medium, minimum nitrate levels for each recipient. Average value observed from all of the results might be one per gram of nitrate. There's variation and batch to batch variation among excipients. These three box plots show the variances grouped on the various suppliers. Each color box plot is for different supplier. If we look at the results of the magnesium, the code on the far left on the red have two nitrate levels around 1PPM. However, supplier code VCM in gray on the right has a high variation and higher nitrate levels. These differences are between different suppliers, potentially reflect the differences in source materials or processing methods for excipient manufacturing.

4A shows the distribution of nitrate results. These results show a wider distribution, the vast majority is much lower. It is important not to say whether it has a high or low

nitrate levels. The contribution of each excipient in the overall level or formation is proportional to the ratio of that in the formulation composition. Box plot B, takes the nitrate results and demonstrates for example, solid or formulation. The nitrate contribution is greatly affected by the overall recipient loading. I would like to end this presentation by sharing some of the plans that the consortium has for 2022. This data sharing initiative has achieved and learned a lot over the past 18 months but our main goal is to continue to grow the data base. We still require more data to help us answer questions on the source and levels of nitrate in excipients. The consortium hopes to increase their understanding on the analytical challenges of testing the excipient nitrate levels and we would like to continue efforts to publish work where possible, to share the knowledge with this data base to the wider scientific community.

>> I would like to acknowledge all of the members within the consortium. We could not have done analysis or gathered this data without the help of everyone in the consortium so thank you for your efforts. Finally, thank you for your attention. And thank you for inviting me to speak to you today about this data sharing initiative.

>> Hello, everyone! Good afternoon! I am sure you have heard of the drug recalls due to the nitrosamines impurities. They are carcinogenic and need to be controlled at a low level. In fact, any nitrosamines for which no toxic data is available, needs to be controlled at or below 18 milligram, which is the acceptable daily is 18 nano gram. Now, nitrosamines impurities can be in drug product and drug substance. In drug substance, they come from manufacturing processes but in drug product, it can form during the manufacturing and also stored. It can possible to control the impurities in the drug substance by modifying the process steps, for example, implementing different synthetic routes, et cetera. But when nitrosamines form in the drug product, it cannot be parsed. So the best way to mitigate this risk is to stop the formation in the first place. Our research has demonstrated, it may be feasible to inhibit this in solid doses formed and in solution. Let's look at the chemistry from a very high level. We need two ingredients, nitrate and -- in this case, I'm showing the secondary. Nitrates when they react with acid forms the active agent NO plus or for that matter, N203. This reacts with the secondary one, to form a nitrosamines. We should remember that, the optimal PH to form it is around PH3. So at that PH, nitrates can react efficiently to form nitrosamines but nitrate

can also directly react with secondary, in prejudice after formaldehyde. They can also form -- although, the rate is much slower than the secondary. Another thing to know, is that nitrate is not a problem for us.

Usually, if we have nitrate as impurity in a drug product, they will not form this under the condition that most experience. So in summary, we need two ingredients and we may link it which is most of the time, a secondary and when that happens, when these two ingredients are present in the drug product, they can form and in drug product, we cannot purge them when they form so we need to (inaudible). How can we do that? What is the mechanistic pathways? In our research, what we did is we exploited two.

The first is the consumption of the active nitro sating agent and the second is the consumption of nitrite. There's two mechanistic we exploited which is the first one is the redox and the second is radiation. In this case, for the redox pathway, I have shown here, is ascorbic acid and for the second pathway, we used the inhibitors where it contains a primary amino group. And for the second mode of this, the consumption of nitrite, we used Polly inhibitors which react directly with nitrites to consume it.

To show the feasibility of the formation in solid doses forms, this was chosen as the model drug. These are the innovators we use. Now to say what we did, we used this as a model drug and made 100 milligram tablets and we made three types of 100 milligram tablets. The first time there's no inhibitor spike in the first type of tablet. In the second type, we have one percent inhibitor spike on person, about 1% and then the third, we had 0.1 percent spike. And to make these tablets, we used these common recipients.

From your previous talk, you know this contains nitrite as impurity. That means in our tablet, we had hydro chloride and nitrite from these. Which means we have both of the ingredients to form them in a drug product. What we did then, after making these tablets, we subjected them here. This is a very harsh condition, but we didn't want to wait a long time. So we wanted to stress them very high, very harsh and see whether our inefficient mechanisms really work. Here is the data.

The tablets containing no inhibitor formed 345 parts per billion in one month. But the tablets containing all of these

five, they formed in a lower level. In fact, if we calculate the inefficient, efficiency of these innovators, we can find that all of these inhibitors, inhibited it in greater than 80 percent level. When they have a spike at 5.7 micro moll level. So if we think of acid, it's like a 1 percent spike.

This is quite remarkable. With this efficiency, we can basically achieve the goal of acceptable daily intake of nitrosamines, no problem. To calculate that, we will achieve this goal. With most, if not all drug product. Now, this is what is shown here, this is inhibition in solid dose form. What happens with at the solution and suspension? We mark it drugs too. So for that demonstration, what we did is we used the same drugs and this is the re action we used. This is a very optimal reaction condition to form. And in this case, what we used are these three amino acids. All of these three, being the amino acids, they had free NH2 primary amino group presented in them and we know from the previous slide that when this is present, the inhibition mechanistic pathway goes through the digestion. We already found that all of these jobs did a great job. Glycine, and -- this formation was at greater than 90 percent level. That means, we should be able to inhibit this solution if we use the proper inhibitors to do the job. In summary, it can be here in multiple pathways. Our model demonstrates this is possible both in solution based products. There could be more pathways available and more research would be needed.

I would like to acknowledge the contributions of my colleagues without that, this project wouldn't have been successful. I thank you for your attention.

>> Thank you for the introduction and good morning, good afternoon, or good evening depending on where you are participating from. I am Martin from Apotex and I wish to thank the FDA organizers of this year's initiative public workshop, especially for the opportunity to participate in this session on the ongoing and challenging issue of nitrosamines. I will share with you three areas of investigation that are worthy of sponsorship and could fruitfully inform policy on the control.

FIRGS, complex nitrosamines are almost all data poor species when it comes to carcinogen studies. They are left with little tools to establish the accessible intakes and have to rely on the read across approach, and research alternative

approaches for AI -- is needed. Second, I would guess most of the people attending this panel discussion today are aware of the causal connection between species in recipients.

However, the extent and kinetics of reactions among these in a given drug product is not yet predictable. This is another area where research could assist with establishing control studies. Third, tertiary APIs are more numerous than secondary APIs which we are well aware of being acceptable. Though direct this tertiary amines is known in the chemical literature, the react conditions are quite forcing for this to occur. Research into this, under typical drug product manufacturing processes, is warranted. We are now well acquainted with what we term the simple nitrosamines and I have four simple examples. They have an acceptable intake value on pharmaceutical products. On the other hand, the finding of complex nitrosamines, dubbed NDSRI has greatly increased since July 2021 when the public was first made aware of this.

This is all the source of recalls since then. Almost all of these complex acceptable understandings because the species had not been subjected to the animal studies. This brings us to the first area that urgently needs further research in policy development. Mainly, establishing a non ad hoc process for acceptable intakes for the carcinogens. Drug product must be informed by quantitative acceptable limits. This is quoted from the control of the impurities in human drugs, FDA guidance.

If nitrosamines without published AI limits are found in drug products, manufacturers should use the approach outlined in ICHM7 to determine the risk associated with nitrosamines and contact the agency about the acceptability of any proposed limit. This is an eminently reasonable requirement of the guidance. However, it is very challenging to Tim MREMT. Unlike the simple nitroSA means that have published limits, almost none have been subjected to animal studies and certainly none for all of the newly discovered nitrosamines in drug products in the last couple of years like the examples I provided on the previous slide. So this leaves them with only toxicology read across to arrive at AIs for complex nitrosamines they encounter with their drug products.

Public domain information, what does the current picture look like with read across vis-  - vis empirical access. The Y axis is the 50 percent lifetime risk tumor dose for what is plotted. The lower the value, the more potent the substance is

and TD values are directly proportional to acceptable intakes so you can view the values as being equivalent to acceptable intakes. Please know it is a logarithmic scale spanning five orders of magnitude so the things in the top of the plot are about 100,000 times less potent than what is on the bottom. The X axis -- the blue circles are the values for all of these listed in data base. About 86 of them have been subjected to animal carcinogen study between the late 1960s up to the 1990s. Only 3 of these are related to APIs. The rest are non API chemicals labeled for context. Nitrosamines appearing on the top are deemed non carcinogenic by the study authors. There is a relationship between increasing TD50 versus the molecular mass of the nitrosamines. The difference between them will cause a variation in potency and this makes the plot look messy. To make the trend easier to visualize, the black squares shows the mean between all grouped in bins, 50 atomic mass units wide. Please note, this is a conservative mean that heavily relates the values that are the most potent. The black squares shows the higher molecular mass tends towards high TD50 values. In other words, lower potency. The thick blue arrow is the typical range derived from small molecule APIs. Importantly, the reddish orangish diamonds are the publically available read across established since 2018. Again, this is a hypothesis. If one considers, especially those examples that appear at the higher molecular masses, they do not reflect the empirical data when considered on mass.

Further research into establishing alternatives to standard read across is urgently needed for complex nitrosamines. This slide was presented in the technical conference and I'm talking about it here to talk about the control strategies. The main point from this slide is that levels of MDMA that have been found in the metformin is higher than the levels based on the amount of precursor, or DMA that was present in the metformin API. In fact, more levels were possible than actually observed.

The first explanation that jumps is there's not enough in the drug product to convert all of the DMR rent. Let's hold this thought and come back to it shortly. They investigated the formation in their API process. Nitrate and NDMA levels in their excipients and in their drug product processes and packaging. It is very informative paper. And I encourage you to read it if you have the opportunity. The main conclusions of the paper are, first, metformin API is not a significant source of NDA but a threshold level of DMA in API is necessary for an adequate control strategy in the drug product. Second,

nitrate levels and excipients are supplier dependent and the dominating factor for NDMA in these drug products. Thirdly, inks and lidding foils can lead to elevated NDMA at higher temperature and humidity.

Not withstanding the excellent investigation, when the precursor is present in the drug product, the question remains for drug product control strategies. Where are they? What are the micro space -- in the respected raw materials and do they have micro scale mobility over the shelf life of the drug product?

That question remains as well relevant as it was last November. To illustrate that point, here's another plot. These show the theoretical form that can form in their XR and IR products respectfully based on the levels they measure from the different excipient suppliers.

I have super imposed on these plots, the maximum amount they measured in the two products, especially in the case of the XR formulation. The levels actually present in the drug product never come close to the amount that could be theoretically generated. Even when the supplier excipient with the highest level is used in the formulation. This paper shows in the case of these metformin products, the amount generated in the drug product is consuming only a small fraction of available DMA and nitrate precursors present. So although measuring and controlling the average content of these precursors will be a component in these strategies, understanding what limits their reaction to form this in the drug product is an important area warranting GDSR funding.

There is a vexing question about the precursors. Here's the real example. In had March of 2022, a manufacturer of the muscle pain reliever, recalled their product due to unacceptable amounts of this and dubbed MMOA. This is a tertiary amine.

And at the risk of direct -- is being deposited by some regulators. However, this drug is considered to contain impurity C, the corresponding secondary amine. Did one, the other, or both of these potential precursors generate the complex drug? I don't think this is yet known. But some regulators are starting to ask that question. Another mechanism by which the complex SDRIs could be forming tertiary amine drugs is that deoxidation is occurring in a trace level by an independent pathway and the secondary amine of the API is in the drug product. We the industry, and FDA alike have to be

concerned about knowing the real significance or insignificance of tertiary means to the drug products because about 30 percent of APIs are tertiary amines. This is the third area that is of great benefit to investigate through the GDSR funded research.

To sum up the points I presented today. GDSR funds would be well allocated towards developing cost and time efficient methods towards AI determination for data poor complex nitroSA means that are less dependent on the precautionary principle. Second, understanding the micro spatial distribution of nitro sating species in excipient SZ and amine precursors when there's impurities and APIs to better predict the formation ken in theics of the simple and complex nitrosamines in drug products and third, establishing whether this is nitro satable in drug products to any meaningful extent or if it's predominantly the trace impurities being nitro sated. I hope you have found these points useful to consider and I look forward to the panel discussion to follow. Thank you for your attention.

>> Hello, my name is Jan and I'm an analytical chemist with FDA research. In many presentation, I want today share with you my prospects of analytic call methods of nitrosamines analytical methods. This has been expanded greatly to not only include simple, but also complicated drug substance related to impurities as well as simple nitroSA means agents. This was the focus of early method development. This nitroSA means have been well studied in food industry, environment science and experience and knowledge from these areas greatly facilitated development in pharmaceuticals.

Later, it became clear that the impurities would not limit to simple ones. For example, a drug that is secondary amine and it can form an impurity. This relatively larger and more complex would require --

With an increasing need -- formation such as nitrate presented -- also became of interest for an analysis. -- different requirements for their respective analytic method. Although, we share one common aspect. We developed methods in order to be highly sensitive in order to detect this interest that will represent in a low level.

With the expansion of this, at analytical platform is greatly moving and expanding. With respect to the instrumentation, the GC mass has been the primary way was

initially the main platform for a lot of this MDMA, MDEA and other simple nitrosamines. This was next utilized. First, to address some unmet needs by GC mass and subsequently became a common platform. With the necessity of analyzing these impurities, this will be utilized in more applications.

Not surprisingly, the mass spectrometer is the detector of choice as an analytical platform due to the high sensitive and selectivity. Due to this is the most common and popular mass approach. Long considered as an invaluable tool for identification and characterization, especially for large biological molecules. This has not typically been utilized. This is used for the analysis. And illustrates the advance of not only being a characterizing tool but shows the progress in using a high resolution mass spectrometer for more -- regulated testing. The use of the internal standard for -- we would like to say, the use of the external standard has become more acceptable and common. The four analytic procedures in this analysis are a good illustration of the analytical platform expansion. Each of these four procedures is unique in the separation technique. Mass spectrometer detector, and quantity approach. The purpose and the design of the analytical methods are deeply effected by the regulatory policies. The FDA published guidance and information for the industry regarding the contamination. As well as the general information has shaped the scope. The requirement implies the need of highly selective and -- method. Determines the minimum that a particular method needs to achieve.

Physical methods for this analysis can be susceptible to many pitfalls as they are designed to detect and quantity very low level with a complex matrix. These obstacles can lead to inaccurate measurements in unfounded. Having a separation, detection, and quantity and knowing well, how these aspects affect each other is critical to develop a suitable and robust method. A few examples from our experience or literature is provided to underscore the importance of a wholistic approach or method development. The first example is the choice of separation detection. GC mass is the most common technique for this analysis. However, it's wide an application does not necessitate the applicability to all samples. This relies on high temperature for separation detection. Some APIs like relative to here, may undergo some degradation to form this as a result of the process.

Application of GC mass, therefore, would result in the report of artificially high levels as shown in the example

here. The MDMA measured with head space, was over 2,000PPM. Compared to some PPM with LCMS. So in this case, although GCMS and LCMS is there, LCMS is more suitable because it does not involve a process until after the separation of -- from M DNA. The second example is the lack of selectivity from instrument parameter settings. Mass spectrometer and detectors have the great benefit of adding additional selective through magnesium such as multiple reaction monitoring, high resolution or accurate mass. Or the combinations and reduce the dependency on promoting the graphic -- to achieve the native selectivity. Still, the resemblance to other molecules in terms of chemical structure and molecule mass, through the compromise selectivity of the mass spectrometer if not, properly handled. The example here is application of LC high resolution mass spectrum for the analysis of MDMA in metformin drug product which may also form this NDMA as a residual solvent and this shares a similar mass and molecule structure. With MOT rad selection, the method depends on the high power, this is an isotopic peek with appropriate to achieve -- of NDMA.

A lower mass power setting would lead to the overall as showing where they represented in the blue bar which is generally more higher than the FDA's represented by this for the same sample.

For the sample preparation is a critical component of the analytical method. Its important is often connected. The two fig years here is from the 2021 publication reporting this. The common extraction -- for this method, for the determination of MDMA in metformin. They also find this by the precursor of NDMA which is also an impurity in metformin can react to trace amount of nitrate when this is used as an abstraction solvent. Both of the figures here show a difference between the levels in the samples, extracted only by the methane only and the sample size extracted from -- the addition of scavenger following this abstraction in which it was concluded that a scavenger will water wash may gain the risk of this formation in sample preparation.

Here are a couple of my thoughts on the matters. First, with the increase need of risk assessment and the interest in investigating and mitigating risk, there will be a demand for highly selective and -- method which is continued to expand the use of it. Especially LCMS. For example, an LCMS method was recently developed in our lab to screen nitrate level in different excipients and drug products. LCMS is not of the usual technique of choice but during the course of method

development, it was for that LCM had the advantage of higher sensitivity and flexible for sample preparation XAURed to the conventional technique for nitrate analysis. This analysis is mostly following the approach of targeted able sis. Because of the low level presence of this group of -- by this approach, the identity needs to be known first in order to develop a method to find it in a sample. Would it be beneficial if we adopt non target, in some cases?

By a non target approach, we did not need to have a prior knowledge of the -- and we may be able to simply screen a sample to look for any find them and use that information for the risk assessment. Moving to this approach, it may still require additional enabling technology in the development of new methodologies. With that, I will conclude my presentation with my thanks to the workshop organizer for the opportunity and for my ODR colleagues who have been working together on nitrosamines products in the past few years, thank you for your attention!

>> Good, afternoon. My name is Bob and I'm in the office of generic drugs and it's my pleasure to talk about the research opportunities that exist for nitrosamines in pharmaceuticals and specifically focusing on the pharmacology toxicology area or the safety assessment area. I would like to start with the disclaimer. This represents my views and not FDA's views or policies. The presence of nitrosamines since 2018, after it was identified in a drug substance. Since then, various nitroSA means have been identified across various drug substances as well as drug products, with various root causes for their formation. Now, despite an extensive publication history, there are numerous data gaps that exist when it comes to root cause as well as mitigation of the nitrosamines. In my presentation, I'm considering conventional ones such as NDMR and MDEA as well as the substance related impurities such as these and others out there as well. These compound specific risk assessments and all of the data necessary to conduct the risk assessments for these compounds is not necessarily in the existing literature.

What we know is that nitrosamines are probably human carcinogen and are in different potencies and we need research. Further work is needed used sensitive analytical methods. Further work is done on the risk factors underlying the nitrosamines formation as well as strategies to mitigate it in drug products. These first two sub bullets are topics that my

co presenter wills be discussing in their presentations. My focus is more so on the safety assessment slide including, that further work is needed on the endogenous as well as exogenous exposure of nitrosamines as well as their metabolism. In addition, we need further research into assessments of potency of nitrosamines. Specifically various conditions for experiences that are aiming to characterize their potential while a battery of studies is necessary to category ease it and then the potential for methods that might classify nitrosamines with regard to the carcinogen and also, predictive models. Ultimately further research and collaboration on the chemistry and drug formulation areas is essential as well as for the risk assessment of nitrosamines. This is absolutely critical in advancing generic drug development and ensuring continued access to safe and high quality medicines. The FDA held a workshop including a panel of nitrosamines subject matter experts so we can better understand the research. They have highlighted that our exposure to it is one area that needs further research. Because there's a knowledge gap when it comes to endogenous formation or formation of nitrosamines within the body.

Specifically, we don't know which nitrosamines are formed and in what levels, and this prevents comparisons with levels detected in drugs. They noted that endogenous formation is difficult to characterize. For example, with rapid metabolism, complicates the quantitative determination of nitrosamines levels. There's an unclear rate and fate and excretion of intermediate metabolites to help inform the nitrosamines exposure. We have little information on tissue and organ metabolism other than that the liver, which is low characterized. In addition, there's still uncertainties under DNA repair capacity and the contributions of exogenous and endogenous formation of nitrosamines to those. Exposure to exogenous from, food and water has an additional risk and that needs further investigation. In addition, the potential for bio transformation of nitrosamines can also inform their risk for the mute potential. We need more data. So ultimately we can form models that will predict bio transformation of nitrosamines in the future.

The evaluation of the MU genic potential is another issue. After root cause analysis, sometimes there's one that warrants further safety assessment and in that, mutant is the first step in hazard identification. So although many are mutagenic, it's understand, they vary in potentially and some may not be. We need more research to characterize this using the current

standards for testing sometimes, different conditions and in particular, because there are these data poor NDSRIs for which there's no published literature but we can looking to generate data so we can better understand the mutagenic and carcinogenic risk of these compounds.

So we're interested in optimizing a testing battery to evaluate this. Particularly when trying to establish this a compound is not mutagenic. So a standard bacterial assay, can be informative top identify the potential of the nitrosamines. In fact, many are positive in a standard AIMs test and in those cases, further identification of the mutagenic potential is not really warranted. However, if it's negative, it's not necessarily sufficient to conclude that a compound is lacking mutagenic potential. And that is in part because literature suggests there's species specific differences in the metabolic activation of the potential newt gents such as nitrosamines in the AIMs assay. So there's current and planned research efforts at FDA to investigate mutagenic systems. Some involving mammal cells as well as TGR models. And so, the mutagenicity evaluation is something that and they're collectively looking to add to the overall body of work that will, ultimately help to inform the mutagenicity. Toxicology is another area warranting other research.

A read across may be needed so we can determine an acceptable intake. Now, FDA toxicology subject matter experts look around it as an important factor when accepting a reference compound and there's several research areas that remain to be explored including structured activities, relationships to identify structural features that are mitigating versus activating for mutagenic and carcinogenic activity S. Structural methods for a class, similarities, models to quantitatively predict TD50s as well as models for prediction of metabolism. While progress has been made on risk assessments, there's several areas that need more research. Specifically, I would like to highlight the AIMs assay and follow on the in vivo and in vitro as ways to warrant further consideration. In addition, on the computational toxicology side, models for identifying reference compounds for predicting the carcinogen and a potential already classifying this also warrants further work. Research on efforts on how to mitigate as well as streamlining safety assessment is absolutely key to advancing drug development.

We view collaboration with international regulators as well

as our counter parts in the industry, as a key to advancing this very important work. I would like to finish by thanking the organizers of this workshop as well as the moderators of this important session. I would like to thank each of you for your time and attention. I very much look forward to the panel discussion. Thank you!

>> Thanks very much to our distinguished speakers and I would like to introduce two additional individuals who will be on our expert panel. Please welcome two more people. I'm going toe start off our discussion with the first question to the panel. This question is, can you share with us your thinking on how the toxicology research areas that you have mentioned, how should we prioritize these and if you could, lace them in three buckets, short term goals, intermediate and long term goals, some takes longer than five years to accomplish.

>> Bob: Yes, I would like to address that. The research priorities should be prioritized according to their utility for industry regulators to conduct these assessments. Let me explain. In the 0 to 2 year time frame, I think that Ames optimization and predictive surrogate analysis are key focus. They will go have to go through these sorts of analysis. Some of that work is ongoing. Some is a result of collaborations, ongoing collaborations and I would highlight Ames and the models as important 0 to 2 year priorities. For the two to five year region, I would say the in vivo to in veto is better to have an understanding of the exogenous, are important but may take a while to resolve. The reason I say this is because many of those compounds that undergo predictive models as well as in vitro assays, they may be positive so we need a good surrogate analysis but some may be negative. A smaller portion is negative. So we need these follow up AS saids for that number of compounds and so we need research to streamline what analysis it's under going in the two to five year time frame. So long term, I would say from a broad view, we want a system to categorize nitrosamines from low, medium and hypo ten SI system. And in addition, just as important, we would like to streamline the compound specific risk assessment and that's going to be the models that can predict mutagenic potential as well as carcinogenic potency which is a standard way of getting a surrogate or reference compound. We need the optimal Ames conditions for in vivo analysis and then, TREEM line well defined batteries as non mutagenic in those assays. Thank you!

>> Thank you, I just want to see if our panelist have any additional thoughts. Martin, your hand is up.

>> Martin: Thanks, I can lower my hand here. But thanks for summarizing the view towards research directed around potencies and you have laid out this window. Where do you see or how do you see when such models are developed, to predict either just mutagenicity or potency, how they would be clarified as the gold standard with long term carcinogen studies? Do you see a role for that? Has the agency thought about how it could be managed?

>> This is valid point. We need models and they need to be validated. Some of this work is undertaken by the experts from industry and academics who are looking at all the of the existing data and there should be a cross validation. Essentially our models that are predicting should also be some what in an agreement with the empirical data we have on hand in decades of research. So I think, absolutely, we do need to validate that with some of the existing carcinogenic data. We know it's time intensive and resource intensive to create new data. So we're best off leveraging. And you know, determining the relevance and using it to validate.

>> I have a question, there was a nice presentation about using antioxidants so if we have to result to that or other formations to inhibit the formation of nitrosamines impurities, this may be needed as a reformulation effort of the current product. Can this be used to bridge the bioequivalence of the new and old formulation as part of this effort? And is there any research possible in that area?

>> Thank you! I hope you can hear me well. So this is very nice question. I want, before I answer this question, I want to reiterate, we're trying to understand the potential implications when antioxidant is added to the formulation of the impurities. So if antioxidants do change the viability of a drug product, the agency may have more recommendations to the generic industries depending on the evidence we collect over the years and through the extent of potentially implications. So the agency may require additional studies to ensure that the addition of antioxidants are not going to change the viability.

Now, to your question regarding the use of modeling and simulation. We always, we do know that modeling and simulation is very handy not only for generic drug developers but also for

the regulatory agency. We see a model approach like this and the agency always welcomes it if the proposed approach -- we do acknowledge that, modeling integrated approach can be cost saving and may offer a better process. So when the model is suitably verified, the model can be use the to identify formation difference, for example, before you add the excipients and after you add the excipients so the potential can be identified through the periodical modeling and we can define the formulation safe space to clarify more. It is the product attributes within each drug product variance is expected -- another potential use of the PK modeling is to establish viability using the virtual subjects that can also be -- to summarize your question, yes, I do see this has a role in the virtual environment. Thank you!

>> Do any of our other panelist have any thoughts? This next question is for a few of our panelist. Let's start with Martin. You talked act secondary and tertiary means. What are the efforts ongoing to better understand or what should be the efforts to better understand it so we can rank the list of ingredients to form these NDSRIs?

>> Martin: Thank you, I can do this answer in two parts. First for the amine precursors. I think, the real challenge as I pointed out in my presentation too is when it comes to tertiary amine APIs, almost invariably, there's one compendium of the non -- at least on the stoichiometric basis. The amount of that secondary amine impurity is more than sufficient when the corresponding nitrosamines are being detected to account for all of it being there. So the real challenge is to figure out whether in fact, it is always an only secondary amine impurity, that is the principle source of the corresponding nitrosamines discovered or if it's -- I know, I'm posing a question here but this is really where the experimental efforts lie to disentangle these two things. Historically, the industry was not looking at trace minor reactions of that nature in drug products. That focus is intended to be more in the area of API. So that's on the amine precursor side. So nitro sating agents. Though in principle, they can come along with the APIs, let's take an example of a secondary amine API like the (inaudible) example that has been spoken to here. You presume for the most part, that if the nitrite were agent in the API itself, we would routinely detect the significant amounts in the API. It seems as more and more information comes to light, that the presence of these complex nitrosamines in APIs is often negligible or absent. So they're

not present in the API. They are really forming essentially, and completely in the drug product. So the area of research there is really to try to determine for a better word is the same nitrate measured in a drug product, how much of that is available to react with the precursor amine?

As summarized in the presentation on the paper from the Merck researchers is that, of all of the nitrate present, only a tiny fraction is converting and it's not DMA limited. So that is really an important area because we will be seeing, and I think, Grace presented earlier saying, if you took all of the excipients that they have been testing, there's a mean level of 1PPM in the typical common excipients that are used in solid dose drugs but it looks like as more information is coming out, only a small minority of that reacts. That may still be a problematic amount with respect to the acceptable intake but we really have to get a handle on what are the conditions under which, you know, one percent of the nitrate reacts versus 0.001 percent. That's the important area to consider from the chemical standpoint in the coming months to years.

>> Thank you, and I see, Kausik, your hand up is as well.

>> Kausik: Thanks, Martin! This is a challenging problem to ascertain whether the nitrosamines we're seeing in the product, whether it's really coming from this or the secondary immune impurities. We thought about bringing simple solutions to experiment, specifically, you take your secondary amine and subject it to nitrate under the exact condition like PH3. Quite a lot of nitrite overnight. You would expect your secondary amine would really make a lot. You quantity that in the end of the day. Similarly, you take the corresponding amine, subject it to the same solution state and see what happens. Sometimes you're surprised, here, you're forming 80 percent with secondary amine but with the tertiary amine in solution state conditions, you are only forming a certain percent. So in that case, there's an argument to be made. That tertiary amine, now, you can calculate that. This is the reactivity difference you are seeing in solution state. If the similar react deference. You have applied in solid state taking into account how much nitrate is there and assume all of the nitrates are reacting. Then we can come up with a number of worst possible scenarios of nitrosamines formation and that could be a (inaudible).

>> David: Maybe to further that point, in terms of secondary versus tertiary amines. The substantiate, smaller amounts like

groups are more likely to cleave, I suppose, then larger such as longer groups. There are larger scale groups so that is probably another thing that needs to be looked at in terms of that research. Another part that is the freebase versus the acidic salt. Whether that has an impact and whether the actual molecule itself, we have seen with some substrate work that we have done that in certain cases, it will form instantly. But in other cases, it will take weeks to form. And there's a solution state where additional nitrate, is again and again and again. So in any case, the nitrosamines don't form and it goes to a number of site products so it does come down to the type of molecule that you are nitro sating which does make it a bit more difficult to clarify what the risk is and how it's going to come. This is more than we had talked about previously.

>> Andre: I have a question from the group. I was wondering, you said you collected nitrite levels, but did you do nitrate? And is there any correlation between the nitrite and nitrate due to the redox dependency and possible conversion of nitrate to nitrite? You know, can you talk about that?

>> Grace: Yes, sure. Can you hear me okay? Great! So yes, the consortium decided it's well worth collecting data from nitrate and nitrite when possible. As early on, we really didn't know if it's useful so as much as we could collect, the better. So with this analysis, we can have around 50 percent of the batches were tested for nitrate at the same time and about 35 excipients so we did an analysis to see if it really does, the nitrate then, is affected and there's no correlation found between the small bit of analysis. So this is something we can keep an eye on as we collect more data but that's how it's common stance.

>> Andre: Thank you!

>> King: I will take the next question and this is for Jan. What is the mode for nitrate KWAUNification by LCMS?

>> Jan: Thank you for the question. I think the LCMS is kind of like a really attempt to apply some of these sensitive -- like, solve the problem. So we're using the mix mode. Like we use the AI exchange. Something like that. So we can also use like the -- in order to increase the confidence. And I can give you a recent paper published by Grace and they have talked about like, the relevant method for this presentation detection and that's kind of interesting.

>> I think the work you talked about, to reduce the nitrosamines in APIs, that's very informative. Is there any side reactions that could entail, like, micro addition products? Like, did you also do some investigation? Like, with these antioxidants, like --

>> Kausik: Thank you for the good question. We have not investigated that. We have a view of it but the problem is that, I the study we did, this was really unreal. But we want today do it just to establish the proof of concept. So if we see something there, sometimes you may see something there and you cannot really say it is realistic and you'll see it in your product. So we know what we have seen, little bit, not much. Something. And there could be a follow up later on but we have not done a methodological study on it yet.

>> We have a question related to the toxicology assessment. So what are some approaches that could be used or should be explored for identifying acceptable intakes for the data poor nitrosamines? So regarding approaches, while we're looking towards some predictions for appropriate reference compounds, that's sort of been our standard approach. We're relying on the standard Ames as the next line approach for determining this. And then after that, we're looking the in vivo with the end points specifically as the current thinking of what we need in order to qualify the mutagenicity. Regarding exposures and so forth, and even occasionally, you know, justifications in the likes of which Dr. Ailer indicated with molecular weight and potency and so forth. Those are informative though at this early stage, we're still looking at those as to whether they're truly validated and reliable sources for determining the compounds. So we're looking at the predictable models and the assay of the current state.

>> Andre: I have a question and not specifically at any specific panel member but we have a lot of ingredients with secondary means and we know some are less reactive because of stearic or so forth. Is there any evidence to develop a quantitative risk model to better rank the relative risk of these drugs to formate SRIs in drugs? What is your answer? Why don't you take the first shot at this?

>> Kausik: Okay, thank you! Sometimes you get lucky because we have seen a secondary amine and now we understand why it was not forming nitrosamines. We subjected it to the character reaction in the pollution state and it does nothing. With the

structure of this molecule and so forth. So that's why I have to say, you have to be lucky. At that point, you can simply say this secondary amine will not form nitrosamines or enough in a drug product.

>> Yea, I just have a follow up, can we develop a general model? Should it be worth any research efforts?

>> Kausik: I think it's worth developing it but for that, we need proper selection of molecule structures. Just from that, you can get your empirical data and then develop the predictive tool. That's why it should be very well done and be studied but it should be done and it could be done.

>> Andre: Martin, do you want to add anything to this?

>> Martin: Yes, there's definitely motif that do not nitro sate, despite the most forcing conditions to actually derive it. Our experience at Apotex, there's some that don't form under conditions. So I can add a cautionary note to everybody on the panel and whoever is joining the conference today, just because a chemical supply house is offering a reference standard of that compound, doesn't mean it actually exists. So I will just leave it at that.

>> Kausik: Thanks for that.

>> Andre: David, do you want to add anything?

>> David: Yes, just to agree with Martin there. The other thing is that, with regards to maybe to Martin's discussion on the secondary impurities, sometimes they're not easily found and they need to be (inaudible). So another issue is the reference standards and generating them for the complex, especially for the impurity risks that we're seeing for the secondary Ames. That leads to a lot of time consuming work because they obviously need to be characterized then. Then the secondary and then, further on, nitro sate. So it can time consuming work that we're seeing now, there's a lot of these impurities that will need to be generated and so there's a lot of work at a lot of labs even in the moment to synthesize these before we begin the analytical testing. That's all I have to add.

>> Jan: Yes, I fully agree with the panelist. I feel most of the study with this, is like, in solution state. So how does that translate to solid state which is the drug product is

aimed at. And I would also wondering, when we do these solutions and can we also do like a screening from this API and then, gather results from this screening and then correlate that to our observation and solution and action and could that be something kind of built from here? And built something? Of course, I would think that's part of it that takes quite an effort. To know the chemical structure and the computational tools to assess the wisdom.

>> Andre: Yes, what happens in the solution state and solid state is very different. That is very true. Yes.

>> King: I have one last comment and we're out of time so we need to wrap up our solution.

>> Kausik: Perfect! It is important to understand how nitrosamines form and what is the formation in solid state and in solution. And there are, I can tell you this much, there's works that have been done on model systems and I hope it will be published in a few months and that those things will be quite good. Helpful.

>> Andre: Yes, thank you, looking forward to the publication.

>> King: Thank you for our speakers and panelist. We hope you found this session useful and engaging, thank you!

>> Thank you so much to all of our speakers and panels of this last session. We really appreciate all of your input. Now, we'll go to our final coffee break of the day. It will be a short five minute break returning promptly at 3:40 p.m. eastern time in the United States for our last session of today's workshop. Sub session 4B, characterization of excipients for complex dosage forms. We'll be back in about five minutes.

>> Rachel: Welcome back! Thank you for joining our second session.

>> Thank you, Rachel for your kind introduction. Welcome back, everyone! I hope you all had a short but highly refreshing break. My name is Wen and I'm a senior advisor for innovation in the strategic office of research and standards. Office of generic drugs. I will be moderating the last session of the day. Sub session 4B, characterization of excipients for complex dosage forms. In this sub session 4B, we have two brief presentations followed by a thirty minute panel discussion. Presenters and panelist will discuss the

challenges related to the detailed proposition of excipients and considerations impacting how excipient identity can create impurity and other factors may influence critical material attributes and impact the potential interchange ability. Actually, quite a lot of work has been done with Polly acid, as POGA polymer. People may ask the question, what other excipients meet this level of detailed characterization to aid in generic drug development. So in this session, our presenters and panelist will share their insights about these topics with us. Our first speaker of this session is Dr. Thomas O' Conner. Dr. O' Conner is the deputy director of office of research, pharmaceutical quality and is a member of CDER's emerging technology team. That answer and participate regulatory challenges through scientific approaches. Today, he's going to present characterization of excipients in complex dosage forms, FDA highlights. Our second speaker Dr. Donna, is an analytical expert from Dr. Ready's lab that has over twenty years of experience in analytical research. Currently, he's working as a lead structure characterization and analytical expert for complex products. Today, he's going to present characterization of excipients for complex dosage forms. Without further adieu, let's welcome Dr. O' Conner.

>> Dr. O' Conner: Thank you for that introduction. My name is Thomas O' Conner and to start off our conversation today, it's MRI pleasure to share highlights on FDA's program on characterization of excipients. In today's short presentation, I would like to share a few highlights that cover a few different areas. First, there's projects that address Q1 sameness assessment for polymer excipients. Second group of highlights will focus on the development of new in vitro release test that can be used to determine the impact of the complex drug performance. Finally I would like to mention -- to address polymer recipient characterization challenges. The goals highlighting our progress that help frame the subsequent presentations and discussions on the remaining challenges. What do we need to focus on as we look out over the next five years. PLGA is a biodegradable polymer that is used on most formulations. These injectable micros need to be qualitatively and quantitatively the same as the corresponding LD. This can make the Q one estimates challenging.

A number of these challenges, methods and other methods are several key characteristics including weight, weight distribution -- ratio and incap analysis. In addition to this, polymer structures can impact product performance. For example, linear or star shaped -- this can help fill the gap

-- with 4 times the systems. To achieve the desired released kinetics, that it may remain a different.

And or different LG ratios. To over come challenge, a research project can different content based on the solubility difference in different solvents. These are just some of the highlights of the number of advancements in the characterization of PLGA polymers in complex drug products. I would refer you to an article on FDA's research program as well as research and science reports for additional information and examples. Another polymer that has been examined as part of the research is listed here, this is used as a surfactant in some. This is available from a number of different manufacturers under varying trade names. They are non active, formed by reacting these. Depending on the process, controls and ingredient specifications, the chemical structure and corresponding properties can be described as this range. How to assess the small variations, impacts this sameness. The approach adopted is on characterizing the properties of the PEG. Based on the understanding of the role of the PEG in the formulation, the characteristics could be identified. In this case, it's the critical my cellular concentration. This looked at the different PEG grades and found in the steady grains that ha similar ones.

This may be important dependent on the drug product and how it's induced. In both the previous cases, the heterogeneous nature pose Q1 sameness questions. This has an impact on these performances. In vivo release test can be important to compare the product performance and discriminate which properties impact the performance. And IVRT can be important when these interact with the manufacturing process impact performance. The FDA research program has advance a number of novel methods to characterize this. In one example highlighted here, adaptive fusion, a pressure driven separation method based on the principles of tangent flow, from the particles such as emulsions.

The method can be optimized based on the formulation. The adjustment of the filter, the cut off, feed flow rate or back pressure. This can provide discriminatory -- mycells and small, medium motions and significantly faster time frame. This method has the potential -- to further examine the impact of the manufacturing process on drug distribution and release characteristics of other challenging complex products. For example, formulation components can be on the cut off range of the membrane. This case, protein bound drug -- to select the

retention process is help -- (inaudible).

By using the advance adaptive adopted user. The impact can be studied based on these and then evaluating their effect on the drug release of the resulting product. In another example of the research funded program, an IVRT testing method was developed that -- simultaneously monitor the disillusion and changing particle size distribution. Injectable suspension that occasionally have various rations, which can impact the clinical outcome of the drug product. This is controlled by the formulation design by including API particle size. This increases the long term product and physical stability. However, this influences the size, it impacts on the disillusion and constantly viability and therapeutic of the product should be considered. This is a complex phenomenon that has different conditions like, particle particle interactions.

In the suspension formulation, this process is controlled by the use of wetting agents. Typically surfactants for the repulsion and by varying the PH. This is a reversal process that is impacted by the sheer stress of the system. In this study, the variation in the injection method applied here, for these, alter the state of the particles and subsequently their dissolution. This team measured dissolution and show that it fall differently in pathways. The final area I would highlight is this. AF4 has a class of field flow fraction nation techniques. They are all based on the same principle. They have without the presence of a stationary phase. These are a wider operational range as a number of experimental factors so size, compatibility, and greater separation power, especially for Polly diverse samples. In this project, AF4 was characterized which has been used in opoid formulations for abuse deterrent properties. This is not stable and may degrade under conditions that may be manufactured in the stabilization process. This is important and the high molecular weight and dispersity characterization challenges. Traditional characterization methods, size have limited resolution and dynamic range. So a new characterization method, based on AF4 was developed. The AF4 method was developed considering the conditions for low and high molecular weight. And implemented the cross flow program to achieve this. It was found that it can be serve add an orthogonal method that is less than one million. This provides a better calculation that results for a larger polymers compared to SEC but there's still challenges noted for ultrahigh molecular weight region which may require further development to address.

We have applied for other challenges programs including the characterization of globular size distributions. While I was only able to enter some highlights over the past few years from the research program, I think there's some general themes posed by the characterization in complex drug products. First, the understanding the properties of excipients and the role and formulation can inform their characterization approaches. Then depending on the complexity of the material that needs to be measured, novel analytical approaches may be needed. Then in addition to raw material properties, manufacturing and post processing can impact the micro structure and the performance of the complex drug product. Discriminatory in vitro release at the times that can facilitate the assessment of the impact of the manufacturing process and post processing on the micro structure. In closing, I would like to thank everyone, FDA and across the network and I look forward to the discussion on the remaining challenge and we with should focus our efforts going forward. Thank you!

>> Good evening, all of you. My name is Dama and I'm working as a lead analytical research development. It's my pleasure to be here to present my experience on a few of the critical excipients characterization in complex dosage forms. So it is essential to understand the Q1/Q2. They should have the same as the tough RNA including the critical. Q2 is the number used in the product which should be -- and excipients and quality and concentrations may significantly impact the finished product but for example, the difference in buffers and compositions may change. Difference in this -- mutually impact the product performance. Hence I any major changes need to understand and understand the impact on the quality, safety and efficacy.

These are a few of the examples of these. Each of the product contains at least one in the products. There could be more than one. Recipient as well. It is a process that is very challenging as well as the justification of Q1 and Q2 aspects. So basically many of the polymer recipients, degradation with time. So for example, as you can see, a few of the smaller molecules are sorted. And some of these -- on the update and then also, it's important aspect to understand the molecular weight, et cetera. So during the formulation process of modernization, there's the degradation of changes in the polymer properties. Hence, it is very challenging to

understand it and some of the critical excipients have variabilities which poses challenges for characterization quantification. As we quantify as part of Q2, many times, the reference product, having a tendency of the water perm nation which leads to variation in Q2. Hence, it is important to understand these changes with time. And to get the accurate information out of Q2.

Another important and very challenging thing is challenging the activities. This comes with different molecular weight and different degrees of substitution. Understanding the right type and right grade is really a challenge with the sort of technique. And another mega challenge to industries lack of techniques such as solution, coupled with the multi angles -- connected with the mass to get the thorough characterization of the polymer recipients and overall, it is very important to understand the chemistry of the molecule to understand the behavior of the excipient in the product and also, the total characterization of the excipient. And as an example, like, this is the molecule of this drug where it is widely used in oral, ophthalmic and oral. This is very important to understand the right tool and also the grade that is essentially -- to understand. And if the industry, if the sum of the company doesn't have the right detector for quantification. Uses of the same standards which is very much similar to the -- essential to understand the right implementation. To understand this, this is very much essential to have. Similar molecular weight standards which gives the similar radius properties.

An example as shown here, this is like, the -- having the same types when the substitutional changes. So this is one of the characterizing techs which is used. This is used as a quantification tool and this is quantified essentially, with the importance of the requirements of this -- for this. These conditions which are used for the quantification. Once we understand the right quantification, then the important aspect is, R we have to use the right grade for the -- of the basically to get the right response.

So to get the right, to understand the molecule right, here, we use this detector to understand the molecular weight distribution profile of this. This was used with the -- to minimize the interactions in the column so the challenge here is once we understand the molecular weight. So then the right standard can be used for the quantification.

Another challenge is once we understand the molecular

weight. For example, as you see here, there's several that have the same weights and there's an ambiguity which, is like, which grade do we use? If you see all of these, they're close molecular weight. The sub TUS changes based on this. And hence, this is important with these products so although we understand the molecular weight and distribution profile, and -- can be used to get the right profile, when there's no standards required for quantification. And as several presenters said, with similar compositions so the degree of substitute is very important to understand. So I just use this as a tool. When we run this, with -- we can see these signals from the group. Where the average number is calculated from these ratios and each grade has a very unique number based on that, the quantification be are developed. And the type of polymer is understood.

To summarize, it's important to understand the right grade with the right substitution using the solution coupled with the scattering depiction and as this. So as another example of a case study which I will be presented on this polymer which is -- degradation. This makes different fatty acid chains. So to use the right tools for this, this is very important to understand that the extent of the degradation for this. So this is the LCMS profile of the different polysorbate so we see, upon understanding of all of these, the quantification can be understood and easily estimated.

The main challenge here is it under goes degradation do this is one of the major challenges and also, polysorbate comes with different grades which is basically, the high purity which is, basically like changes in terms of the slightly fatty acid compositions. To understand the grades, an important tool can be used is the detector. And the peak profiles, it can be easily under the base analysis with this, to get the fatty acids -- these are experimental conditions that we use to separate all of the peeks and based on the peek ratios, it's easily understood which can be used in the product. Overall these are some of the techniques I have just highlighted to understand the quantification purpose of different excipients using different techniques based on the availability of the laboratory can be easily used and then to get the accurate information of the excipient.

So the role and current challenges to summarize and also to understand the future directions, the selectivity and the specificity is very important when it's important it use add least, this to prove the selective technical selective and how

very specific to the -- in the light of interest. And all some of excipients, it's important to understand the accurate quantification and the degradation is also important to understand, to get compensated to get the actual original competition of the product. So based on our experience, the scattering along with -- the best choice for characterization of these attributes of all of the Polly material and it's important to understand to have a suitable standard for quantification in case the polymeric materials, otherwise, the response under the peek may change. And also, ensuring the variability of the standards in case of conventional techniques are used we're going to see the difference in time.

So the analysis is differential -- is important. And so that is where we can correlate the data with the example and understand better and use of these techniques is very very important. At least a couple of the techniques can be explored to understand and cross verify the data based on the certain aspects of each of the molecule. Another important aspect but none the least, is the development of right skill set on all of these analytical techniques. Thank you! So if you have any questions, I would be happy to take them.

>> Moderator: Thank you, you will be joined by additional panel members for a discussion. So now, let's welcome our panel members. Deputy director of DTP1, ORS, OGD, FDA. Dr. BREN Dan, R & D, deputy director, OTR, OPQ, FDA. So first, I will take questions from the chat box in morning. There are two questions from to Dr. O' Conner. The first question is more review related so it may not be best suited to be addressed here so I will have Dr. O' Conner to address the second question.

That is, how many batches of proposed genic will be tested for this? Does two batches of each product suffice. Please go ahead.

>> So I think, I think what you heard with both presentations is some of the challenges with polymer excipients is it can be -- and you even heard some additional challenges where they can change over time based on the degranulation or absorption. So this is a principle why characterizing multiple batches.

From a research perspective and where we focus is developing the analytical method to better understand that. You know, the property and the validation and you know, I want to highlight also in this talk here, to the in vitro method

that can tell you how much that variability is going to impact your performance. I think this is aspects that are really important and this is why generally you need the most multiple batches and generally, you have maybe three additional batches depending on the range you had before, maybe it would be needed and you know, I think we're interested in kind of developing the tool to help the research program to help sponsor and execute that both from analytical and in vitro test methods.

>> Thank you, Tom! Does anyone want to chime in?

>> Brendan: I would rem, the more, the better because bots to bots, you can get some variability to the work that you have gives you a better chance to match exactly the reference product so what really is a matter of as many as you can possibly do, I think, really gives you a better data set.

>> Yes, please go ahead.

>> Dama: It all depends. It depends on the attributes. Like the impact on AVR, et cetera. Where it is very important, and essential to understand multiple lots of the product. For example, the micro dose. This comes with a wide range of molecular weight. And it is very much attention to understand the multiple large R & D and then to be falling in the R & D range. Although, this is very similar. So that is where we can use the multiple ways to get the wide range of the R & D window and in some of the cases like where it is just the quantification where even though you use one or two, getting this lifetime is very important.

>> Wen: Thank you, Dama for your comments. Yes, now we have another question from the audience. If polymer molecular weight is determined by the excipient supplier, oh, there's another question, actually. For Dama. Some of the excipients are composed of several I ingredients. How are they described for these excipients in complex drug products?

>> Darby: My answer is if they have other components, is that kind of the question?

>> Wen: Yes, some are probably composed of multiple components, ingredients. So when we evaluate Q1, Q2, Q3 similarness, how do we evaluate the sameness which is composed of multiple ingredients?

>> I think that's an inherent challenge no matter what. It's

reverse engineering the excipients because it's backwards engineering. We need to find the components and show the reverse engineering where you have the individual components as was shown in some of the ways to parse these out and show the individual components and the relative amounts and how you have that information to support that Q1 sameness. This is actually with multiple parts to it. And then based upon that, you can then, oh sorry, and then based on that, you can then use a Q3 sort of characterization of what it's doing for the drug product. So this is a great way to understand how it's working together. Thanks!

>> Amin, did you have anything to add? If not, we can go to --

>> Sorry, my mic was muted. Thank! I just wanted to add about Q3 similarity of this complex excipients. So some of these excipients are mainly used in typical drug products and some of the ingredients to impart certain characteristics to the drug product, that may not be for such drug variability or for permeations for the skin. So it might be more important for Q3 characteristics to determine what is a critical ingredient in this, as well as high we can identify its role and formulation and its role for drug remediation or local availability after the application to the skin. In this case, it may be easier to understand sort of the role and how to quantify this.

>> Thank you! We have another question for Tom. How do you supply, supplier to supplier and lot to lot should be evaluated in the types of advance techniques you're looking at before these properties can really be tied to any types of conclusions as to impact?

>> Tom: Just trying to understand the question a little bitter. I think, what we're trying to do, I think, in the program is to develop methods that we can getter characterize the excipient and then testing multiple examples, with lots of variations or different standards, different grades, you know, to help us understand what the natural variabilities are. And then looking at that, and then when we're talking about where I go with control going on or performance, I think, is getting impact that, I think that's when we try to compliment it with our understanding on how this material works with the formulation, to understanding the chemistry and then B, can we develop in vitro early test methods or characterization methods that can test these ranges and see where we can have a discriminatory power on the impact. I think, coupling these two togethers will help us connect variability for the impacts

on the performance.

>> Wen: Thank you. Tom. Would anyone like to add additional comments?

>> Brendan: It comes across the presentation but it's really between characterization and performance. Quite clearly, you can have an excipient that exceeds but of course, it's important what exactly it is, and it's important to have the particular rate and the test, to assess the performance. And once you have a quantity, you can start thinking about performance and making similar formulations and then test that and then ultimately building up the specification because I suppose when suppliers are sending in materials, then you need to assess the ranges that they're supplied to and whether or not that range is too wide or whether that range is a little tethered. Obviously the characterization and the in vitro performance needs to go hand in glove for these more complex formulations. I don't think it's a one size fits all as Thomas said, you need to marry these three things together.

>> Darma: I do have a question on what was mentioned by Tom and Brandon. So these, this is very important to understand the physical attributes which is basically the properties and then like, what may play a major role in terms of variability and even the small will have an impact on this variability properties and the micro structure and solution. So these important points when we're trying to change this and you know, so this is a very important aspect of it.

>> Wen: Thank you! Yes, we do have quite some questions coming in. Actually, this question is for FDA panelist. How can we have better standards for excipients to be used in our drug products? How important is it for FDA to partner with USD and other standard setting organizations? Yes, maybe, do you want to start commenting on this question?

>> Sure, Wen. So as our international agency for characterization of complex recipients and for the new complex. This has -- with USB and we have also, like, meeting with EMA and this is regarding the other excipients and, regarding upgrade or updating these methodologies. So we are working on this at all time.

>> I would follow up on that one too. The inherent challenges, especially with the complex excipients, another thing you hear

about is the identity or how we standardize becomes more challenging. What kind of properties do we include in that sort of monograph or specification to say this is a standard or meets the standard. So these things that might have a wide distribution, especially when we're looking at the aspect of ultimately in the drug product house act. So there's kind of that balance there between the two to get that standardization but also, what sort of things to include in the standard and ultimate understanding on how it's going to be used is probably a little bit more important to how it acts with the drug product. So there's a combination of both. But I think there's kind of a drive and that kind of emphasis and need for these standards and complex recipients.

>> Wen: Tom, do you want to chime in?

>> Tom: Yes, I think it's very important in the labs and developing local methods that are critical for the work that we do. You know, to the point, what are we trying to task and that might influence what kind of standard we need. Is it molar mass and so I think, this is available and more standards are helpful because without it, we don't have the right methods but yes, we need to make sure we identify what we need and I think, it would be beneficial to develop these methods if available.

>> Wen: Thank you all! Yes, we have another question for all panelist. The question is, how is analytical variability of the method factored along with the variability to determine the suitable attribute range to target for the functional excipients in the test product?

>> Dama: I think it should be -- as possible. I think it's very important to look at what kind of information we're getting. Whether it's quantitative or qualitative information which is the relationship. And we're developing a method. Second important aspect is to ensure to see the data and how much is a map between the two techniques to understand within the technique variability. And also, it is very much important to understand, using the same. If we can test it on this, as well as like -- adopting how much is there. So this is essentially used, the variability within the methodology, how much it is. So that is like, when we're looking at this quantification aspect, what is the kind of variability that is limited?

>> Thomas: I would say it depends on the variability. If it's small variability, that method is not good and it's not going to give you the informing you need to you have to keep that in mind. How to work hard to produce it and, you know, it might be something you need to develop to encourage you to get there. So it really should be -- (inaudible).

>> Darby: What the previous speakers said is very wowed. Also, having a lot to -- part of this is to make sure that the method is precise. As well as any aspect of the standards. You have not just one standard but you can develop others to make sure you have the precision to test that. So I think there's factors here, sort of the hand in hand, how you can do this to fit your purpose and how much variability is sort of the excipient has to test it. These are two critical things.

>> Wen: Thank you, Darby. We have another question. Maybe Tom can help us like, how does the evaluation differ for a use of a co process excipient versus the regular administered type of excipient? Yes, that's have very good question. Whether it's a co process or a mixture of the excipients.

>> Tom: Yes, with those cases, we haven't really taken a different approach, you know? So I think, with the characterization and the Q1, like, to give up the individual component. And take a look at that. That's a process, API. Yes, like, excipient. And just understanding what is in there and then, again, how this is playing with the simulation. Sometimes you can do that, but -- whether it's manufacture ability or performance or some other aspect. So I don't really have a good answer about anything different, you know? This is just case by case.

>> Wen: Yes, I want to ask our industry panel members, do you have any experiences in characterizing this process versus just the mixture of excipients?

>> Brendan: I'm thinking as long as they're a physical mixture and not chemically blinded, I would echo Tom's point, it shouldn't make a difference unless it's chemically designed, you should be able to separate them and so forth. I don't know if Dama has any experience with it?

>> Dama: I think it's very important to understand the structural aspects of the components as you share, sometimes,

this can have a secondary interaction like hydrophobic or any sort of process and it can fold into, you know, more of a stable form and it lead to a viscosity change as well as even sometimes, the molecular rates can change when compared to the physical when there's a minimum reaction between the excipients so that's one observation we can see from some of the ophthalmic products.

>> Wen: Thank you, Dama for your comments. Now, it's 4:30. I see that we can wrap up this session. I just want to thank our speakers and the panel members again. For your excellent presentation and discussion. Now, we can conclude our session and conclude our first day of the public workshop. Thank you all for your active participation. I hope you have enjoyed the first day program ranging from the next five years of the generic product science research program, model integrated by approaches, excipient impacts as well as well thought public comments. And you can watch the YouTube videos of the presentations today on the center for complex generics channel. Please subscribe to this channel for updates about trainings, workshops of complex topics. Tomorrow, the workshop will start at 8 a.m. with a very interesting session. The global nature of the generic industry followed by implementing science in product development and ANDAs, drug device combination products and ending with a panel discussion on the next five years.

You can find the agenda details or slides on the FDA website. Hope to see you all at the meeting tomorrow! Enjoy the rest of your day. The meeting is adjourned.

BIS-FDA-Fiscal Year 2022 Generic Drug Science and Research Initiatives Workshop
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>> Welcome to our second day of the GDUFA public workshop for FY22. Allow me to welcome people from across the globe. It is our pleasure to welcome you here today. A few housekeeping notes that the agenda for the workshop and the bigraphical information is posted online and we welcome you to refer to that throughout the day. The links to that will be provided in the chat and we'll update that throughout the day as well. We very much value your engagement through this workshop and so we welcome you to submit questions using the Q & A box and you can do that throughout the presentations and panel discussions and we'll try to address those questions that you send in either through the text box and response or to the best extent that we can, we'll try to put them in our panel discussions as well. You can also submit any comments or other questions you may have, particularly comments to the docket that will be kept open for about a month after the workshop and because we

recognize this workshop is happening in time zones across the world, we also have a YouTube channel that is hosted by the center for research for complex generics and that channel will be making available for live streaming all of the presentations within minutes after the presentations for each session has broadcasted live.

Also, transcripts and recordings of the entire presentation will be available on FDA's website after the meeting. With that said, let me say we are very much looking forward to your participation in the workshop today. And allow me to welcome Dr. Sarah who will be kicking off our first session of the day. Dr. Sarah is the associate director for generic drug global affairs in FDA's office of generic drugs where she develops strategies to address, identify emerging regulatory challenges in relation to the international nature of the generic drug industry. In collaboration with other offices, she has stakeholder engagement and harmonization of regulatory approaches for generic drugs. She's received advance degrees at University from Cincinnati to Cairo and has had a distinguished career in academia industry and the FDA where she spent the better part of the last decade. Please join me in welcoming Dr. Sarah.

>> Sarah: Thank you, Sam for the kind introduction. Good morning, good afternoon and good evening, everyone. I'm very excited to be chairing this session. Our session today is totally inspired by the global nature of the generic drug industry. Now, we as regulators are constantly optimizing our structure in the complexity and diversity of the products we regulate to ensure that global quality and safety demands are met. We have an excellent and a very global list of speakers and panelist today. Starting our session off is Dr. Michael. Then we'll talk to Dr. Bill about the challenges in clinical development for orally inhaled drug products in the United States and Europe. And then with the expansion of bio waivers and global development of genre products is professor Leslie who is a chair in the sciences in University of San Francisco. Professor amine will talk elements of modeling and simulation may support global submissions and professor of systems pharmacology, University of Manchester and senior vice president of research and development and chief scientific

officer. From the European perspective, Dr. Susana, medicines from Europe will present on the single development that is a key to unlocking access and my colleague from AMA, Dr. Kevin Blake, the senior specialist at EMA who is also the scientific secretariat for the working party since 2015 and he'll be providing us an overview of the challenges and opportunities for global development. And then my dear colleague Wenlei will talk about how can scientific advance wants help align global development of complex generics products. She's a senior advisor and innovation and strategic out reach in the office of research and standards in OGD. Without further adieu, it's my pleasure to switch it over to Dr. Michael Banks.

>> Michael Banks: Hello, I'm the global head at the pharmaceuticals and I would like to give a brief introductory presentation about some of the challenges of current challenges to complex generic drug development. So on the agenda, I will just briefly talk about how complex generics can more easily access if there's more global harmonization. How reciprocal agreements can work, how flexibility and processes and procedures could help. Briefly talk about predictability, consistency, some of the communication opportunities, and then give a brief conclusion and recommendation.

The CRCG published results of a survey in which respondents were asked about harmonizing related to complex generics. 94 percent either agree or strongly agree it's important to harmonize international approach to help get them approved. However, the initiative report noted another challenge marked in generics and a lack of foreign competitor. We all know that Canada doesn't require fasting and fed drugs for others and Europe doesn't always require steady state studies for long acting ingestibles. Adoption of these more globally can get them in more markets, more quickly and for less cost.

Reciprocity, we all know global regulator have made strides harmonizing framework and increasing inspections on many years. We have peeks and other mutual recognition agreements. Surely now it's time to apply the same method to premarket reviews. There are many complex generic products on the market in Canada, in Europe, but not yet in the U.S. patients in these regions are getting the same high quality, generic drug for many years and seeing the benefits of that also, the healthcare providers are too. Surely sharing an acceptance of application reviews is the next step. Regulatory flexibility ANDAs for certain types of complex formulations, must be QQ to be received and approved by FDA but things don't have to be that

way. An equally safe and efficacious dose can be delivered to each patient with non QQ formulations. How to allow for more flexibility in demonstrating QQ? We see now the discussion that is going on about improving our idea which is a great step but we know it can be very challenging to find the most appropriate IID entry to reference and that can lead to multiple exchanges with FDA. So what can be learned from other countries and regions with regard to how they accept different formulations for complex generics.

Predictability and consistency. One of the surest ways to significantly delay or shift investment away from the generic drug development program is any agency to change its advice. We have seen QQ issues being raised in second or third review cycles and no formulation changes require investing millions of dollars in MU investment activities and that changes the business case for investment potentially. Regardless, it will lead to many delays in patient access. For years, and in some cases, the whole program may be abandoned. Product specific guidance, FDA's revised multiple PSGs and applied them retrospectively to end this already under review. It puts that program back many many years in most cases so I'm really looking forward to the improvements under ANDA GDUFA 3 specifically under PSG. There's other ways to harmonize when there's conflicts, when there's conflicts between the USP and ISO. Surely improve coordination with other global regulators will yield more online policies and definitely bring complex generics to our patients much faster.

Communication opportunities. Parallel scientific advice is a good program, a good step forward but more could be done. European approach tends to be more flexible and looks at the merits of each individual application. Product specific guidance is very much prospective, whereas in the U.S., it's retrospective. I think the hesitation with regard to PSA is that no one really wants to end up with the highest common denominator. Communication and transparency needs to improve between FDA and sponsors and there really needs to be more of a willingness to accept alternative approaches per NDA. The standards aren't really different between Europe and the U.S. if the complex generic products are the same within the regions, that's the most important thing. I think CRCG will definitely help define acceptable approaches and alternative approaches which is very important.

Put it this way, if FDA has a potential device it changes and can result in a generic being abandoned by the sponsor, how

should FDA weigh the risk of not having a generic? Think about this and how can this action be more openly communicated? So I said my presentation would be short. In conclusion, the approval standard for new products is a reasonable assurance of safety and efficacy, not an absolute assurance. And FDA has ample ample experience, making benefit risk assessments based on the science and merits of each individual application. One size does not need to fit all with regard to any generic product. The agency needs to apply similarly flexible approaches to complex generics. And their reviews to rapidly improve patient access. The industry fully appreciates the role of the GDUFA regulator science program and we're all very much looking forward to the improvements in GDUFA 3 and moving the needle up on the complex generic reviews but in the mean time, let's improve collaboration with other regulators. Elements of their review programs, use their regulatory reviews and that will undoubtedly result in faster patient access to complex generics in the U.S. thank you!

>> Thank you, Sarah for the introduction and to the FDA team to invite me to present generic challenges during a clinical development of orally inhaled drugs in context to U.S. FDA and EMEA guidelines. Considering this short time frame, the next fifteen minutes, I will primarily focus on the generic cycles which are definitely not distinct and have been discussed in various regulatory and pharmacology forums yet, we have not seen any outcomes which is basically a little bit discouraging. These challenges have come from, you know, a lot of experience and I believe these are the primary reasons which it discourages the global generics to venture into this territory of drug development, especially of orally inhaled drug products. This is my disclaimer. A fairly wordy slide. To cut the long story short, these opinions are surely mine and do not represent statements or opinions of SANDOZ pharmaceuticals. This presentation is based on published data. Coming to the contents, this presentation will conclude a con caution of US FDA and EMA pharmacokinetics, conclusion. In this slide, I essentially demonstrate the high level differences between these approaches, versus the EMA.

US FDA demands demonstrates in vitro, farm Coe kinetics and all strengths. This gives us at each stage, if not the PK and then the PD stage before the application gets rejected. These differences, although they look academically intriguing, but it clearly indicates there is no cross talk on the data mechanisms on the U.S. FDA and EMA in context to inhaled drugs. Generics have to develop contrasting strategies for two different

agencies for the same innovator. They didn't do this and they have the same in vivo, and in vitro data for all agencies globally. On the next slide, I'll go to the advance of PK batch selection and clinical end point differences, however, there's definitely a need for harmonization amongst the guidelines to make the life of generic easier.

The differences is that PK is to essentially to demonstrate safety, while the other is for efficacy like interventions like charcoal, block to block absorptions and safety studies which are conventional PK studies. P FDA recognizes BE and all availability strengths for product registration, while EMA usually accepts studies in one strength if in vivo proportionality is established. FDA doesn't recognize therapeutic studies but EMA may recommend studies for children for some products which are essentially used in children as an aerosol. Dose selection in the lower strength in accordance to the FDA guidelines and this is minimum sufficient -- with highly sensitive bio and clinical methods but EMA usually recommends clinically recommended dose which is already there in the product specific guidelines.

Equivalence criteria for both the agencies, however, EMA also recommends an additional T max similarity. For testing reference batch selection, EMA recommends a target batch, plus or minus 15 percent, and believe that in vitro translates to in vivo finding whereas, FDA recommends a random batch approach which is usually a nightmare for the drug development.

In this slide, it essentially discusses the batch to batch variability in the generic development, common irrespective of agency guidelines. A common in vitro starts with the exploratory PK studies, which predict a PK outcome. Our targeted difference is picked to develop a test in similar lines. During the course of development, this gets all or expired so during the close to pivotal PK studies, we essentially don't have a reference and they begin to find another reference to go into PK which requires in vitro testing of various new reference product to define the similar in vitro specification to test and -- the older deference product.

So how minimal in vitro translate to PK differences? Here, I published this on the cell combination of innovator, Advair. With this data, we understand that despite the significant in vitro difference, there is a potential of PK bioequivalence SIs in reference product, indicating a risk of failing the study if it changes in the course of development. These PK bio

equivalencies are fundamental to inhale product development, primarily due to low dose, low viability, including additional complexity of the position trajectories in the lungs. Unfortunately, this issue has been prevailing for a decade and discussed in various forums but no guidelines have been able to address this issue.

Further to adding to the body of evidence to highlight the importance of batch to batch in PK is this statistical experiment conducted by IPAC which gives 64 subject study ins which comparison between multiple batch and single batches are made. In the context of single harmonized design, of two periods, single group randomized cross over study. The probability of bioequivalence is true test by reference, PK reference. And the results indicate that mere 10 percent between batch variability has potential to reduce the study power from 100 percent to 70 percent and in error from 5 percent. Suggesting this single batch approach has non optimal study designs for inhalation products. However, the same study, these errors were significantly negated by adding more number of batches. These results mandate multiple batches and probability of considering widening of equivalent lens limits demonstrating batch to batch variability.

In the pharmacokinetic, EMA is more generalized in its approach. However, the generic industry stops the submissions with PK studies and generally do not venture into PD for EMA submissions due to the significant cost and volume with these studies. FDA says lowest recommended dose to enhance the sensitivity to define the differences between test and reference, along with the demonstrate of the therapeutic equivalence and they both have to demonstrate the super. This is a four to eight week treatment study in a parallel design. With parameters as an end point, while only bronco dilator, especially the long acting bronco dilators are evaluated in asthma or COPD in a cross over single dose design. For the short acting, FDA recommended a study using the E max model with the end points. On the other hand, EMA recommends designs irrespective of the drug's product and are open to more end points such as exhale and spit. A basic fundamental issue with clinical end points in a parallel design and with asthma is a large sample size. In a recent publication by FDA which compares all of the FDA submitted data and defies the variability, 1.286, and 580 plus placebo. This is estimated to nearly 1400 subjects demonstrating a power of 80 percent which you can see here. Plus, another 100 subjects from the placebo arm. This is in the red line. This is driven in a drug

response and the heterogeneous behavior of asthma in terms of exacerbation rates and low dose steroid response in a wide physiological severity inclusion criteria as recommended in the guidelines.

So can we reduce the highest sample size studies? Basically answer is yes. If we can conduct adequately designed dose response studies, or relative potency studies. The major challenges is that spirometry, for these combinations and so, this is data from the dose ranging studies from this drug which is a known steroid and two doses which is recommended are 100 and 200 micro gram available in the market. You can see this cannot demonstrate any significant doses association between 100 and 200. When I take this data together, what I see is that, a 33 percent increase in dose would require to induce the 10 percent increase in response. So clearly indicating spirometry is not the answer. The other parameters such as resistance has recently emerged as probably promising parameters in the management of lung diseases. It definitely has been able to distinguish dose response, especially with the short acting bronco dilators and also, distinguish a central and peripheral drug response. The airway conductance is another parameter which needs concentration and further studies.

So another important area that needs research that has been around for a long time is can FDA follow the EMA way of using PK metrics to establish efficacy? Now, if you consider that this is the same in the section, then elements that could be performance measures for bioequivalence are those available in the lung. And the position geography. It has been discussed in various forums but there's still some areas which needs further research. The GI -- if I take PK studies and compare it with the clinical end point studies, the GI block, PK studies essentially indicate the primary dose. The metrics such as Dmax and the disillusion rate can predict the resident which will definitely need more data and PK studies with different AP sizes may have homozygous, which could have important parameters that could distinguish the central deposition. So in area definitely needs some consider for their research as well.

So coming to a conclusion. There is no strategic or scientific relationship between the FDA and EMA submission strategy, implying rather independent development programs that add to the enormous cost burden in the drug development. There is an urgent need to explore a novel PK approaches such as

multi- batch approach, research designs and statistics for products with high INTER- batch variability as well as maybe considering the RSABE strategy and expanding the equivalence limits for higher inner- batch variability. Clinical trials with high sample size provide expensive problems for generic medicine makers and are a significant deterrent to generic enterprises. There is also a need to create innovative clinical metrics as well as study PK investigations as a method of replacing therapeutic bioequivalence, particularly its ability to differentiate against the positions in the lung areas. These are my acknowledgment. Essentially the whole SANDOZ clinical development team. Thank you very much! I will be available during the panel discussion to take any questions.

>> Thank you, I am pleased to have the opportunity to participate in this workshop and present the expansion of bio waivers and global development of generic products. It's 5:30 a.m. here in San Francisco but I bet a more convenient time for you. I will address three topics for this presentation. First, the history and rationale for the present bio waiver criteria. Second, potential areas for the expansion of drug eligible bio waivers and third, using BCS criteria to predict the drug of a new molecular entity.

So BCS is the scientific framework for classifying drugs based on their aqueous solubility and testable permeability. The guidance in 2000 entitled for in vivo bio availability and bioequivalence studies for immediate release solid oral dosage forms based on the bio farm P classification system. This allowed bio waivers for class one, high solubility and permeability drugs. The revision in 2017 allowed the expansion for class three drugs, high solubility, low permeability and the further revision this past May in concordance with the ICH, changed the basic criteria for the dose relative to predicting the solubility.

In 2017 membership determinations for BCS, initially in 2000, highly solubility is when the highest dose strength, a product approved on the market, is soluble in 250 mils or less of water over a PH range of 1 to 6.8 at 37 degrees. This was a highly soluble drug. The criteria for permeability in 2000 was a thermal dynamic criteria. When the extent of absorption, how much in humans, is determined in 2000, it was less than or equal to 95 percent of the dose, this is changed in 2017 to less than or equal to 85 percent of the dose. If the regulatory agency agreed that your compound met the solubility

and permeability high criteria, then BCH biowaiver could occur with a dissolution class one drug rapidly dissolving with greater than 85 percent dissolved in 30 minutes of one buffer. So the classification in 2000 was a class one drug. Highly soluble, highly permeable. Rapid dissolution was eligible for a biowaiver. The rationale for this is that observed in vivo difference and the rate of extent op absorption from the drug of two pharmaceutical drug may be difference in drug solution in vivo. However, when the in vivo dissolution is rapid with gastric emptying and the drug has high permeability, the rate and extent is unlikely to be dependent on drug dissolution and or GI transit time. Under certain circumstances, demonstration in vivo by BA or BE may not be necessary for drug products containing class 1 drug substances as well as the inactive ingredients used in the dosage form do not significantly affect the absorption of the inactive ingredients.

Note this permeability criteria, thermal dynamic criteria, when the extent of absorption in humans is determined to be more than or equal to 85 percent of the dose, which originally defined based on a kinetic parameter. The 29 drugs initially studied were all shown to have a high rate of permeability which was then shown to correlate well with a high extent of permeability. So the initial development of the BCS was based on rate, but the criteria was based on extent. But that is no longer true. The FDA has classified as highly permeable, a number of drugs where absorption is greater than 85 percent in humans but the perm ability rate is less than that. And at least one in case, this drug here, the permeability rate because it goes through so poorly.

In 2017, biowaiver eligibility was expanded to class 3 drugs. The qualified for a BCS based biowaiver for class 3 substance, both the test product and the reference product should display very rapid, greater than 85 percent dissolved and less than 15 minutes versus class one, 30 minutes. In vitro dissolution characteristics. BCS class three drug substances are considered to be more susceptible to the effects of excipients than they are. And for BCS class three drugs, all of the excipients should be qualitatively the same and quantitatively similar except for film coding or capsule, gel, excipients. Excipients that may affect absorption should be qualitatively the same and quantitatively similar that is within plus or minus 10 percent of the amount of excipient in the reference product and furthermore, the accumulative difference for these excipients should all be within plus or minus 10 percent.

In 2021, there was a switch from high dose strength to highest single therapeutic dose. A drug sentence that is now classified as highly soluble is the highest single therapeutic dose approved in the labeling is completely soluble in 250 milliliters or less of aqueous. This is now defined as PH1.2 as a lower limit to 6.8 at 36 degrees. In cases where the highest single therapeutic dose does not meet the highest solubility criteria, but the highest strength of the reference product, the old criteria, is soluble under required conditions. BCS biowaiver can be supported based on the pharmacokinetics over the range that includes the highest single therapeutic dose. This altered requirement, following the EMA criteria is a valid change but it will decrease the number of drugs eligible for biowaivers since we're at a higher concentration, a higher dose.

Topic two, expansion of biowaivers. Are there scientifically valid possibilities of expanding the number of drugs eligible for biowaivers without endangering patient safety? I believe there are and initially, BCS class two car box lick and are ready go in solution. So without further research, I believe it's and meets the current present dissolution for class one drugs at these P HSHGs. Initially, this is limited only to drugs where acidic PKA result in this. Giving low PKAs.

What about a PCS class four carboxylic eligible if the highest dose is at 4.5 and 6.8 and meets the current disillusion requirements for the class 3 drugs at these PHs as well as the BCS class three excipient requirement. Initially, again, this would be limited only to drugs where acidic PKA results from carboxylic acid. However, here, I believe that further research is needed as the possibility for the class four carboxylic acids can potentially meet these requirements. What about all acidic BCS class two drugs? Those that are not carboxylic acids? Can they be eligible for biowaivers? It may also be reasonable to make all acidic BCS class 2 drugs if the single dose is soluble at PH4.5 and 6.8 and meets the current requirements. Perhaps, the maximum PKA requirement should be added, for example, only drugs with acidic PKAs less than 4.5 are eligible to make sure of the ionization differentiation. Here for sure, further research is needed as to the possibility that class 2 non carboxylic acid drugs can potentially meet these requirements.

My third topic is predicting drug disposition

characteristics of new molecular entities based on BCS criteria. In 2005, Wu and Bennet reported that the drug disposition characteristics of an MME may be reasonably predicted based on the FDA, BCS solubility criteria and the rate of intestinal perm ability. Since it can very clearly differentiate drugs primarily eliminated by metabolism, versus those by urinary and bilary extra reason of unchanged drug. We called this BCDS. So what we have shown is class one and class two high permeability is eliminated by metabolism. However, low permeability rate drugs, class three and four, they are primarily eliminated by renal and bilary. We designated a slightly different criteria BDDCS based on extent of metabolism and solubility as predicted here.

The advantages of the BDDCS is that further predictions can be made. We showed that almost all class 1 high metabolism, extensive metabolism, high permeability, high solubility drugs. The transporter effects even when they're shown in vitro to be extensive, will be minimal in the liver and clinically insignificant. Versus the class two drugs where, although they are primarily eliminated by metabolism, E flux transporter effects in the gut, with both uptake and e flex can ask the liver. Class three and four, because they're low permeability, they need transporters to get absorbed and once they are absorbed, then efflux. Earlier this year, we have now expanded the designations to list 1,475 drugs. But in this analysis, we went and look add at the 191 drugs that also were BCS classified to understand the concordance or lack of concordance, the discordance. What we showed is overall, there's a 68 percent concordance. Quite good for BCS class two drugs. Good for BCS class one and class three drugs. But very poor for BCS class four drugs. In essence, when we recommend is that you use BDDCS in preference to BCS to make predictions of drug distribution. Thank you for your attention and I'm pleased to answer questions during the panel discussion.

My name is Amin and first of all, I want to thank all of the organizers for giving me the opportunity to talk about an elements of modeling and simulation that may support global submissions. As usual, this slide will be available as part of this pack and lists all of my conflict of interests. Perhaps if you cannot remember any sections of this particular talk later on, you should remember only this slide because it summarizes the elements of modeling and simulation that supports global submission. And these are in these three words. Quality, quality, quality. So what is so difficult about achieving global acceptance at the same level because

we're aware, it's not taken at the same level, with different regulatory authorities across the world. The difficulty is what actually constitutes the quality? The trust in the outcome of the studies is not something that is specific to modeling simulation. I draw your attention to the report by Baker in 2016 in nature. When over 52 percent of the scientists, they actually represented significant doubts with regards to reproducibility issue with any scientific work they're basically getting published. If you add the other 39 percent they had slight concerns and they thought that no, we haven't got a significant crisis but there is some certain crisis, you will come up with a figure that is over 90 percent.

So this is not a specific to modeling simulation and it's not specific to certain area. You can see it goes from chemistry through the medicine and everything. And it is also related to reproducibility, not just of the work by others but even the work that is done in your own lab. Of course, there is not just the issue of reproducibility and getting the same result which we can call precision in what we're getting but it is also the matter of accuracy. The more recent report by national academy of science, engineering and medicine in 2019, they actually had a book that is available free online, when they summarized the consensus with regard to different elements of the reproducibility and repeatability. And indicated, in fact, the trust in the outcome of science in all of the different sectors have been going down, apart from scientists themselves and military. I don't know how the numbers for the previous slide might have changed post COVID but let's move to the area of modeling and simulation. I have indicated my views with regard to one element that is related to the robustness and ease of assessment of the models, mainly, open source code.

There are reports such as seen here by the group, that have indicated there are big issues with the ability to reproduce the results that they are coming from modeling and simulation done by such open source code elements. So the open source code models, they come in the form of a blessing because they're open and people can contribute, modify, add to their scientific, let's say, novelties in these models in realtime but at the same time, they come as a curse because of all of those elements related to the robustness reproducibility and ease of assessment and understanding what changes have occurred.

Regardless of the nature of the source code and whether it is open for everyone to go and change the source code or

whether it has got a gatekeeper that only allows certain certified individuals or committee to go and make such differences and record those. You have to ensure certain elements are there for assuring quality and reproducibility. We have summarized these in recent article availability online now in pharmaceutical research. This is Sebastian and myself, where we tried to distinguish between validation, verification, and qualification. We argue why validation is possible for the code itself and accuracy of the mathematical implementations. When it comes to the validation of the general model and its application in PBPK and USP area, this is an exercise. The mere fact of not having the clinical data is the reason why doing the modeling and simulation in these areas. If the data is available, then the model is useless because we already have got the data and we know the answer. So how this, you know, can be reconciled? Whenever we have sets of data that there are matching the outcome that we are predicting with the modeling, this adds to the verification of the model in that particular area but it is not still a validation for the intended purpose of use of certain drug or certain condition in which we do not have any clinical data. And of course, this is again, going through the same cycle.

If we do this in the form of clinical study and validation then why in the first place we needed to do the modeling and simulation? Because we have the answer with the clinical study. Therefore, this becomes a circular argument, we also indicate that the number of the verifications that we are requiring in certain areas increases the trust in the model and gives a higher qualification of that model for that particular area even, it is still not going to validate that for the next intended purpose for which we have not used the model before. This is in contrast, completely to the model creditability recent guidance that has been published for the medical devices by FDA and I explained that in the next slide. Many of you might have seen this draft guidance by FDA with regard to modeling and simulation creditability criteria as applied to medical devices. This was released in December and was open for public comment and until March, which was the deadline for public comments, it received more than 20 pub comments.

The issue of applying some of the criteria that is shown in this guidance to area of the PBPK and QSP is, I will describe it as having a hammer and seeing everything in front of you as a nail. This is picked up by the committee with regard to the certain elements of the guidance that basically says that, these modeling cannot be used as a replacement for clinical

studies while the major purpose of the modeling and simulation as we have got with the biowaivers which are kind of the model and it was previously discussed by other speakers. The whole idea is not to have studies because we can actually predict their outcome. In our article, we outlined the process of getting the qualification and we talked about how this qualification would be sensitive to time because it is basically integration of our latest knowledge. It is the same way that any doctor, pharmacist and so on have to get a renewal for their qualifications making sure they're fit for that particular job. And we also indicated the number of cases and show there's some discrepancies. Many of the aspects that we are talking about, they were similar to what the industrial group of scientists, a couple of years ago. They published with regard to the separation of the platform itself from the model verification for that intended purpose. So what are the issues for debate and discussion?

As I basically mentioned, in the beginning defining the quality is at the moment, something that we haven't got a global agreement on. In the article we indicated that process of introducing changes to the model is something we have to talk about and make sure that there is ease of assessment of such changes. They are easily identifiable. Frequency of recertifying and qualifying the models is something we have to discuss and debate whether we need it every year, every other year, every five years. The number of the required verification cases is something that nobody wants to commit themselves to. This is something they have discussed in private between three to ten cases giving confidence and finally, what constitutes transparency and whether that is needed to be for everyone, over only the regulators or a certain group of people can have access to codes in a transparent mode to make sure that all of these are available without actually bridging any IP issues. With that, I will stop and I will be able to hopefully contribute to some of the discussion during the panel session. Thank you very much for listening!

>> Thank you very much for the kind introduction, Sarah. My name is Susan and I'm a clinical development safety director for medicines for Europe which is the European trade association for the off patent sector. Thank you for joining me today in this supporting conference. The subject of my talk is single global development and how it can be used as a key to unlock patient access to generic products. We're seeing an

evolving landscape for generic development. We have more and more complex products, increasingly complex clinical development programs, niche therapeutics and personalized medicine is a reality and we have to deal with orphan products. So there's a risk of fewer follow on products which entails less competition and less patient access to affordable generics. So in order to address this, we have the goal of offering access globally and tailor development based on scientific discussion. How we can do this is single development of multiple jurisdictions to avoid the repetition of unnecessary studies.

Single global development is the standard approach for the originator development. It's commonly acceptable for biosimilar development and foreign compare TORs is already accepted for generic development by other highly regulated regions and we'll come back to this point later on in my presentation. So the current situation for generic development is the one that you are seeing here where we have independent development processes and programs for the various regions. And what we should try to achieve is a streamline development and be faster access that will allow us to have one comment development for the various regions where the developers targeting to registered this product.

Now, for this to be possible, there are three pillars that must advance simultaneously. We're talking about harmonization of bio equivalent standards, the legal framework and the criteria for acceptance for foreign comparators which combined will pave the way for allowing single global development for generic medicines? Now, focusing on the first pillar, harmonization of global. This is done and the draft of the first international guideline for the immediate release study design is expected to be released for consultation later this year. Now, the goal of harmonization of the bioequivalence approach at ICH is we go from a scenario such as the one that you see here where each jurisdiction has its own independent guideline for the conduction of bioequivalence and design of bioequivalence studies and these guidelines are not always having the same criteria and approach. So once the M13 guideline is available and implemented through ICH, we will be looking at a harmonization and convergence scenario where everyone will be following the same scientific principles to design their bioequivalence program for the immediate release of these products.

Now, harmonization of bioequivalence. Does it matter? We

have talked about this already in the session today. It matters a lot to recent international survey on complex generics as you have seen. It shows overwhelmingly support on the importance of a harmonized international approach for complex generics. Now, this brings us to the second pillar I mentioned before. European and U.S. laws require a local reference law but they do not prevent sourcing of the comparative product from another jurisdiction because the legal text are silent regarding the source of the comparator of the product. So terminology is important. We're talking about two very relevant but distinct terms. The reference product which in Europe and in the U.S., must be authorized in the region and in Europe -- in the region -- is the product that is used in the trial. These are -- so these are the conclusions from the report on single U.S. EU framework for the development of generic medicines and in this report, it states that the statute requires reference product in the U.S. to reference approved brand product but is silent on the issue of whether the studies of the non U.S. version of such reference products can be considered by the FDA in its review of the generic applications.

So U.S. statute does not preclude FDA from determining, for example, that if a reference product is approved outside of the U.S. has the same formulation dosage form, strength and route of administration, has the U.S. approved product is made in a facility or facilities licensed and inspected by a regulatory authority according to standards similar to the FDA's standards? And finally, was it approved by a non U.S. regulatory authority applying approval standards similar to those applied by the FDA? Then that is the non U.S. product can be used in testing and the testing required by U.S. law.

This is in fact, very similar to the approach that is accepted for biosimilars. So the solution is since there is a distinction between the reference product and the comparator product, and there is no legal barrier to using foreign comparator products, then the real question we must focus on is which foreign comparator products can be accepted. This brings us to the third pillar I mentioned earlier in my talk today. The guideline is needed and this guideline would establish scientific criteria and the conditions of acceptability of foreign comparators for bioequivalence and the FDA and EMA jointly or even together with more regions would be tasks with developing this scientific guideline to establish these criteria and conditions. Now, I want to caution you that this is not a new concept. In fact, what I'm showing you in this

slide is coming from an article published in 2019, and already, you can see a number of other highly regulated regions who accept the foreign comparators, including also the WHO. Now, since this article was published, the UK has left the European union and in fact, the UK has join this list.

So many countries have already implemented this. We don't really have to reinvent the wheel. You can see here two examples of guidelines that define the use of foreign comparator products and authorities could build on these very relevant scientific principles to develop their own guidelines for the use and acceptability of the foreign comparator products. Now, the use foreign comparator products will tackle an important barrier to generic development in some jurisdictions which is the difficulty to access the local comparator product and to acquire it to use for the conduction of the bioequivalence studies. So here you can see three examples that somehow are related to this concept. One is from the U.S. another one very recent one, already from 2022 from Canada. And also, an example from Brazil. Now, ANVISA case interestingly focusing on the reauthorization to use the foreign comparator because the local comparator could not be acquired. So this is something very important to keep in mind because the acceptability of foreign comparator and the definition of such criteria would also help us tackle this important barrier to the drug development.

Now, what is in practice is the importance of single development? It avoids redundant clinical trials which has a very important implication, for example, in terms of ethics. It helps increase patient access to generic medicines which is especially important in cases like orphan drugs and complex generics. It contributes to generic competition. It leverages the benefits of harnessing this because even if we harmonize the standards in ICH, the studies still need to be repeated for each jurisdiction in order to use the local comparator products, then the harmonization of the standards cannot really properly be leveraged and benefited from. And finally, it also helps to over come challenges in sourcing the comparative products in some of the regions where this problem is very relevant.

So, what is the way forward? Now, internationally we need to continue advancing harmonization and dialogue. I have mentioned N13 and the guidelines, the first guideline in this series but other guidelines are planned in the M13 series. We also need to discuss harmonization and the standards, for

example, for modified release so this is an ongoing effort that needs to be continued. And then, locally or jointly, the regions and the different countries need to access their legal frameworks and move forward in case there's no legal barriers as the case in the U.S. and also, in Europe. And the criteria for acceptance of foreign comparators needs to be defined in appropriate scientific guidelines. Now, my take home messages to you today. Single global development is fundamental to support global access and global competitiveness. In order to leverage the benefits of harmonization of bioequivalence, the use of foreign comparator products is necessary and criteria should be defined and the time to act is now. So thank you very much for your attention. I am looking forward to discussing further at the end of this session. Thank you very much!

>> Good morning, colleagues! Thank you for the introduction and thank you for the invitation to speak today on the rather broad topic of challenges and opportunities for global development. Firstly to say that standards disclaimer that the views expressed in this presentation are those of myself and are not necessarily of the European medicines agency or its committees. We have heard already this morning about this concept of the use of a foreign comparator product and this is probably going to be the major focus of my talk today. And it's just to introduce by saying that it's mandatory within the European union to have what is referred to as an EU reference product. This is a medicinal product granted by the EU member states by the commission on the basis of a complete agreement, in other words, with the submission of quality, preclinical and clinical data in accordance with the relevant articles of the European directive, 2001/83. It's just to note that an application for an authorization that refers to the generic or the hybrid medicinal product must include demonstration of equivalence. There really is only one exception to this use of European union reference product and that is, if the local product is no longer available and under these circumstances, an application can be made under an article 10A or what is also referred to as a well established use application. And in these circumstances, comparison with the foreign comparator, could be acceptable if that comparator has clinical data for efficacy and safety. I won't go into too much detail on this well established use application. This is also referred to a bibliographical, provided that the substances have been in well established use within the European community for at least ten years and with a recognize efficacy and level of safety. There

are specific criteria for applying under this article 10A and basically these related to well established use within the claim, therapeutic medication which takes into account time and also, the quantitative aspects of the use of the product and also, the degree of the scientific interest and the coherence of scientific assessments and also needs to be already established positive benefit risk balance. And studies can only be provided for bridging to support the relevance of the literature. Now, to move on to more detail in terms of the generics application. Within the European union, we don't commonly use the term complex generics. In the context of phone and applications but for us, this is generally understood as complex generics, we would consider as hybrid applications under article 103 of the directive and this is basically the case where the medicine product does not fall within the definition of a generic as provided elsewhere in the directive and this is usually related to where bioequivalence cannot be demonstrated to bio availability studies or if there are changes in the active substances or therapeutic indications, strain, form, or route of administration versus the reference product. And in these cases, it is usually expected that @ results of the appropriate preclinical tests are or clinical trials can be provided and within the application, applicants have to identify the EU reference product and this goes into detail such as the specific stage where the product was sourced from.

However having said that, I want to highlight there an examples although these are perhaps, exceedingly rare but with hybrid applications, there have been cases where studies with non EU comparator products have been used and supported and an example and the link here is to the public assessment report but this is for a product call. Within this application, the study to meet U.S. registration requirements was submitted and basically, because it was conducted against a U.S. reference product, the data was only supportive but in this regard, they were considered informative for the characterization of the pharmacokinetic behavior and specifically in this case, it was related to the demonstration of linearity of pharmacokinetics. Within this particular application, this data was really, although we say supportive, they were important in establishing the linearity and enhance the appropriate dosage.

So it's perhaps, using this example is to give kind of some idea or insight into what might be an area for further research around hybrid applications to consider and this is the context of studies that might not be directly considered relating to establishing bioequivalence but they are important for further

characterizing pharmacokinetics of a product. And particularly, when compared to reference products and as we say these days, may be possible to use or to obtain from when we would call a comparator product. So for the next part of the presentation, I basically wanted to kind of expand on this concept, for complex generics or hybrid applications. The idea of having a different form and also, a different indication may mean that information is needed on more than just the comparison to the reference medicinal product. And for this particular example I have here today, it's very recently concluded what we call an article 29- 4 or a CMHP referral. Without overly going into the details of this, it's possible within the European union to have a number of routes to apply for a marketing organization, not all of which involves coming to an essentialized route via the EMA but instead, it can be true, what we call a mutual recognition or decentralized procedures via the member states. Sometimes, when there is a disagreement among the member states in relation to the non centralized applications where there are scientific issues that need to be concluded on, the member states refer the matter to the CHMP for what we call arbitration but for what we say is a scientific conclusion based on the available data and within this particular example, it concerns product code called Nasolam which is a nasal spray that contains this drug that is used to stop prolonged, acute, or sudden seizures, but this is a solution that is given IV and it's not used to treat prolonged acute convulsive seizures. So the member states were not able to reach an agreement regarding the use of the medicine for this particular indication. And the main grounds for the referral were concerns about the safety and effectiveness of the medicine when used for these acute seizures in the non hospital setting.

For this particular use, it's just to highlight that the company submitted data for a solution that is authorized in the EU by the name Buccolam via a hybrid 10- 3 application and effectively within this procedure, this drug was used as a comparator product in addition to the EU reference. So among other issues, the CHMP asked the applicant to address the bridging of data on efficacy and safety between these two drugs in view of non similar exposure profiles which are demonstrated in the submitted pharmacokinetic data. This included different exposure and also there was a question around the under dosing and heavier subjects due to decreasing exposure with increasing body weight. And to highlight in the context of a kind of an area for further research, and also the use of modeling and simulation to support applications, I would like to highlight

that for the antiepileptic indication, there was submitted 8PKPD, using pop PK, and pop PK- PD models and these were in adults in pediatric patients in the elderly and in special populations. And dissimulations were performed using this administered and so this is a good example of the use of such data to support indications in this case.

Data from the BUCCOLAM were used to construct the moles of simulations and within the procedure, the applicant also provided literature data to further support the use of adults in this anticonvulsive seizure medications.

So the CHMP considered the available data and concluded this supports the use of it in the treatment of seizures and it was concluded that the benefits, out weighed the risk in these seizure indication and therefore, a marketing authorization should be granted in all concerned member states and there was also further recommendations that the proposed product information should be amended to reflect the available data. For example, these changes related to dozing for older patients and also further instructions for care, under the use of a second dose when treating seizures. So hopefully this example is interesting on a number of levels relating to how the kind of, data to support a particular application may be drawn from multiple sources and as I have said, may not just use data referring to the reference product but also to additional comparator product. And perhaps to be a bit more regulatory about it, the note that the applicants is the procedure and guidance from the European commission in terms of applications within the EU and specifically, within this section I have here is states that for a product which has been approved as a hybrid application, if subsequent applications are submitted for a different product, but which refers to supporting the same reference product, the data that was used to support what we call here, the product B, can also be referred to under certain circumstances to support this, what we call product C. So it's a little bit, seems complicated here but basically, the idea is that you can again, use information that is submitted for one hybrid product to support another hybrid product but basically, they would have to refer back to the same reference product.

To summarize, basically, the use of an EU reference product is mandatory and the use of a foreign comparator is only in a particular setting for well established use. However, for hybrid or complex generic applications, PK data with a non EU comparator could be used as supportive and again, it's just as

concept for such applications, kind of a body of evidence approach with data from multiple sources is perhaps something that we will see more of and to remind in terms of what data might be used to support such a totality of evidence of approach, it is recommended that scientific advice is sought early in development. And while a regulatory question is such is out of the scope of scientific advice, we would tend not to deal with questions that directly ask around the legal basis. However, questions relating to the scientific aspects of the use of a comparator would be considered within scope. And again, to kind of emphasize the pilot parallel scientific advice, that is ongoing with the FDA. And for which we have already heard in some detail. And will hear more of shortly. With that, I would like to conclude and can take questions in the panel discussion later. Thank you!

>> Good morning, good afternoon, good evening, everyone! Welcome to the last presentation of session five, the global nature of the generic industry. My name is Wenlei and I'm a senior advisor for innovation and strategic out reach at the office of research and standards, office of generic drugs, CDER, U.S. FDA. Today, I'm going to present on how scientific advancements can help align global development of complex generic products. This presentation reflects my own view and should not be construed to represent FDA's views or policies. The concept of complex product was introduced in the GDUFA letter. FDA provided a list of complex products, including complex active ingredients, complex formulation dosage form, complex route of delivery, complex drug combination. Here, I want to emphasize, in the context of GDUFA 2, this presents challenges for drug generic development which is difficult to access drug sameness or bioequivalence at the intended site of action.

The nature of product complexity is diverse. Some product complexity is associated with drug substance. Some are with dosage forms and also, different regulatory agencies may have a different classification about complex products. The concept of complex product is not static. It may evolve over time based on agency feedback and experience.

Based on published guidelines and approval from different regulatory agencies, we know that different regulatory standards have been used for the approval of important complex generics or follow on products in different jurisdictions. Some products may have been approved by EMA, health Canada, but

not by FDA or vice versa. Harmonization of technical and scientific standards for generic drugs presents an opportunity for significant public health benefit by streamlining drug development across regulatory jurisdictions and increasing patient access globally to high quality, affordable, pharmaceuticals. Efforts were initiated with the equivalence guidelines, as immediate release, solid dosage forms. As stated in the reflection paper on generics endorsed by this, in November of 2019, a series of guidelines on standards for demonstrating equivalence of more complex dosage forms will also be followed. In the next ten minutes also, I will highlight US FDA efforts especially GDUFA research and global collaboration efforts to over come scientific and regulatory challenges to help development of safe, effective, and high quality complex generic drugs.

First, I have good news to share. About three weeks ago, FDA published the manual of policies and procedures aggregated as MAP on classification of complex products. In this MAPP, definition and examples of complex drugs and drug device combination products were provided. In addition, the responsibility and the procedures for complex drug classification and the data base maintenance are also described in the MAPP. This helps clarify the understanding about complex products and the standardized complex product classification process, making complex product classification transparent to industry and any regulatory agency who may be interested in understanding FDA's complex product concept. This slide summarizes some analytics to highlight the FDA regulatory science efforts to support generic drug development and approval between fiscal year 2018 and 2020. In the following three categories. Development of drug products, generation of evidence needed to support efficient review and the timely approval of ANDs and evaluation of generic drug equivalence.

As shown on the table in the right corner, highlighted in green, the number of ANDA approvals impacted by research has a steady increase from 63 in fiscal year 2018 to 152 in fiscal year 2020. These are solid data showcasing scientific advancements, to help development of genre products. If you are interested in more of this analytics, please refer to this web link for more details. Next, I will SLEKD three complex product categories to illustrate the research focus in each product category at the impact of GDUFA research on the guidance development and product approval. The first is already about already inhaled and nasal drug products as

OINDPS. Here is a cartoon to summarizes the requirements for the OINDPS from different regulatory agencies. The left is the evidence approach and the right is step one approach. U.S. FDA and EMA are at the two opposite ends. PMDA and NMPA is closer to the U.S. approach. TGA is more aligned with the EMA step wise approach.

In recent years, health Canada and ANVISA is shifting widely to the approach. So what is the approach for OINDPs? This is between the generic and the preference product. In device similarity, the generic product and reference product should demonstrate equivalence if product performance, equivalence in local drug delivery by comparator clinical end point, all farm Coe dynamic studies. Not each individual equivalence metric but all should be met in characterizing all aspects of the OINDPs performance.

In contrast to US FDA's suite of evidence approach, EMA approaches to establish the equivalence as illustrated in this slide. Step one, conduct individual equivalence tests. If the equivalent TE is concluded. If not, move to step two. Conduct PK studies with or without charcoal blockage to demonstrate pulmonary deposition and systemic exposure. If equivalent, PE is concluded. If not, move to step three, conduct PK studies to demonstrate local equivalence. As you can see, there is significant difference between width of evidence approach and step wise approach, presenting additional difficulty for generic applicants who -- in multiple jurisdictions.

Put simply, FDA has alternative thinking regarding CCEP or PD studies for OINDP. These studies are considered less sensitive for evaluating formulation differences that other BE methods due to high variability and flat exposure response of these studies.

FDA encourages applicants to propose alternative approaches to the CCEP and PD BE studies. Hopefully these alternative approaches can address the relationship of the systemic PK to local drug levels within the lungs, address the relationship between in vitro performance, to local drug deposition and a clinical performance. These alternative approaches include but are not limited to more than simulation and advance analytical methods for better characterization of the product. Here, I would like to give you an example of advanced analytical methods for better characterization of the product. Morphology directed a spectroscopy, combines these in one integrated platform for substance specific particle size determination.

This method helped determine the particle sizes of API excludeing interference from other excipients. This technique has supported the approval of first generics of this nasal suspension. We will continue to explore this method's potential to reduce some equivalence test for other OINDP. Some research funded by FDA demonstrated that realistic in vivo, aerodynamic, particle size distribution methods incorporating models and realistic range of inhalation profiles can provide a better prediction of deposition of in health particle in the lungs and capture patient variability. Also, in vitro dissolution system such as this system was optimized to characterize with this profile, of this dry powder inhaler and meter dose inhalers. This method can accurately capture differences in formulations. The advancement in vivo studies provide options for alternative approaches to CCEP helps promote regulatory convergence and improve global access of OINDPs.

In topical dermatology areas, FDA has focused on supporting the expansion of the approaches it a majority of topical dermatology products. Developing PK methods to directly monitor the drug absorption, at or near the site of action in the scheme and enhancing PBPK models to predict the drug absorption. Here are some example drug product specific guidances related to topical dermatology products based on the GDUFA outcomes. Also, in recent years, there's a significant number of topical product approval which will help improve patient access to this product at the lower drug price. As of long acting products, there's quite some challenges as well as opportunities ahead of us. Currently no generic version of long acting PLG product is approved by US FDA. The GDUFA research has focused on developing new tools for complex recipient characterization, understanding how raw materials impact formulation characteristics and drug release and exploring more clinically relevant in vitro release methods and others in this research outcomes were translated to support product specific guidance and generic drug approval. To help align global development of complex generic drugs, FDA has been utilizing some platforms, on the international pharmaceutical regulatory program, IPRP to have direct dialogues with global regulatories. In addition, some scientific topics on this were discussed -- initiated workshops among regulatory academia and industry scientists.

In 2021, FDA launched two new initiative including generic drug cluster and FDA EMA parallels, scientific advice pilot program. The generic drug cluster is the first forum

established for the leading agencies to address this globally, aiming to increase scientific alignment among leading generic drug regulatory agencies.

As of FDA, EMA pilot program, the goal of this program is to provide a mechanism for FDA and EMA assessors to concurrently exchange their views on scientific issues with applicants during the development phase of complex generic drug, hybrid products. Through the PSA product, applicants will gain an understanding of both agencies recommendations. Next, I will share with you some discussed topics at the meetings including pin parent -- class considerations, convergence will help the global patient access to these products. Our discussion is focused on pinpointing key differences among different agencies regarding regulatory standards, identified aspects, hindering approval and exchanging regulatory scientific advancements. Hopefully, fruitful exchange and discussion in the generic drug cluster and other global collaboration platforms can serve as a basis for future guideline development of complex products.

In summary, FDA is committed to support complex generic drug development through GDUFA research and through GDUFA 2 enhancements. I hope now you can understand that though there are unique scientific and regulatory challenges for global development of complex generic products, significant regulatory science advancements have facilitated guidance development and approval of complex generic products. Furthermore, global collaborations help accelerate the scientific advancements and help with the development of global complex generic products.

With that, I would like to thank my colleagues at the office of generic drugs, office of research standards, GDUFA regulatory science collaborators for their work presented here. Now, I will pass it on --

>> Sarah: Thank you so much! Truly, thank you to the presenters on an array of presentations that compare and contrasted the bioequivalence standards in different international regulatory jurisdictions, discussed barriers to harmonization and considered what research could produce the information models or evidence needed to over come the barriers and support global alignment. Now, in addition to our speakers that I previously introduced, joining our panel discussion is Dr. Heart, before we start the panel discussion, I would like to call on the panelist. If you have any questions to be directed to the presenters today?

>> Les: I can't start my video. It says it's not allowed.

>> Sarah: Thank you, welcome to the studio. Please, proceed with your question.

>> Wenlei: This question is for Dr. Bennet. Yes, thank you for a very nice presentation and also, a very interesting concept. You proposed to expand it to -- intestinal -- I wondered, did you consider the impact of these both fasting and fed conditions. If the drug cannot disintegrate, the drug may not dissolve properly even know it has good solubility. So I do have more concerns with this class 2 carboxylate, than the one and three drugs.

>> Les: Well, Wenlei, I don't disagree. Further research should be required. I don't really think that's going to be an issue in terms of what happens in the stomach but you know, if we're going to expand it, we need to do the research to figure it out. It was my opinion that the class two carboxylate acid drug, you don't need to do more research. You bring up a good thought and I don't think the studies have been done as far as fed and fast studies, have they? Do you know if they have?

>> Wenlei: I am not aware of the class two drugs. I'm aware of some of the study with the class one drug. Under the viscous media, it may impact the dissolution.

>> Leslie: But I said you have to meet the first criteria in terms of excipients in my criteria, you have to meet the same criteria for the class 2 carboxylate acid drugs that you have to do for the class one I'm not saying you have to waive the criteria but you can and it will be done.

>> Wenlei: Yes, I think if I read your slide correctly, you focused on the dissolution of PH4.5 and 6.8, probably you omit the dissolution at PH1.2. Here, I just want to point out, probably at 1.2, this is important. Thank you! We can discuss more offline.

>> Sarah: Precisely these types of discussions and the research that can allow us to better shape our regulations based on our regulatory environments and Wenlei, I do recognize the fast and fed discussion. This is a critical discussion to have and possibly, significant research being needed in this area. Go ahead. To start the first discussion, our first

question today and this is open for all of our panelist here. Is we do understand the legal barriers to the acceptance of foreign comparators in numerous jurisdictions. This has been touched upon in the presentations today. What development limitations are currently present and where can scientific evidence bridge those gaps?

>> Susana: Thank you very much! This is one of my favorite topics and I'm glad you brought it up. I think what I would like to highlight and I highlighted this in my presentation. But in terms of the acceptance of foreign comparators, what the research to help define the criteria under which circumstances the foreign comparators could be accepted. And here, when I say research, I don't mean it has to be experimental.

A good way to start this is looking at the existing criteria from the regions that have them because there's good ideas there that might be used an inspiration for the other jurisdictions to work on. The other angle would be, as it was pointed out by many speakers. Not only today but also yesterday in this session, during the day yesterday, is this is really an important issue to look at from a global perspective and at an international level. So it would really be ideal that even if the guidelines cannot be issued jointly because it would be outside of the relative of your different agencies, it would be interesting that some form of alignment would start to be formed around this so ultimately when these guidelines can be made available, they would go in a similar direction. So just some thoughts on my side, on this topic, thank you!

>> Siddharth: So after what was just mentioned. We spoke about different routes of application, like, the mixes and so on, while there are instances which they even spoke about where I do agree, foreign comparators were used and considered acceptable, I think we need to look more deeply into how we can have a harmonized approach being acceptable even for 10- 1 applications or 5G. In that matter, this is across group, when we're talking about, like, the market step. So I think this is where the dialogue needs to happen with regulators across the globe in making sure we kind of have a comparable product and not already, not the innovative drug being marketed for the source of this study. So I think that's where the alignment has to be there. That's where the discussion needs to be there in having a common comparator.

>> Sarah: Thank you! Any other panel input? Particularly,

what are the current development limitations that exist as a result of the lack of harmonization of these foreign comparators? I maybe industry's input is valuable here.

>> Susana: Thanks again! An interesting example is in the case of the development requires, for example, that patients are used. In this case, the recruitment aspect of these patients, especially if you have to repeat the studies would be a really important issue to consider because essentially, if the same sponsor is developing the product for both regions and they do need to repeat the study in other populations but essentially, what this means is in the end, they have to prioritize one region or another, because they can't do the trial at the same time for both regions and this ultimately means that the product development would be delayed for a region. So I hope that illustrates the question.

>> Sarah. Dr. Banks?

>> Dr. Banks: I'm just building on what Susana said and considering certain products I have seen over time. So the difference is in one region, you can have 400 -- in the data whatsoever. So this is very distinct. It's not that difficult for more global harmonization to be reached because you have certain circumstances to allow this which can include countries like Canada, Australia, Israel and other markets. Some of the other big countries allow for flexibility and looking at what they do allow and the category of products they allow this to happen, it's not actually that much research but being able to allow that flexibility within the system, within the U.S. needs to be looked at.

>> Bill: I agree with Dr. Banks and the other. One way to look, I think in the presentations, we have also seen that countries like, the Europe harmonizations and countries like New Zealand, Australia and even UK have been joining this, basically, leveraging the studies which have been done in Europe or elsewhere in the country, probably on the in vitro data assessments. Then I think if it's neutral, if your drug matches with some of the local drug. Like, in vitro, I can match a European innovator with an American innovator. Why should we have a different program altogether? So these are things, like, for example.

I'm just giving you an example of like a huge program, a big clinical trial as well and there is, in between, a very tough, I would say, tough studies and it's the most difficult

thing I would pass, to say.

So why not? If we can have these comparison in vitro and we can use that middle part except the PK of Europe and avoid the time delay happening in the PK study. This is a very essential topic that needs harmonization because the generic companies, they definitely get discouraged because of too big of investments to be done. So this is my point.

>> Sarah: Thank you for that.

>> Wenlei: I think the common comparator product is very very important topic for global development of complex generics. There are some challenges. I just want to probably name a few. For some of the complex products, first, I think we need to have approved through the centralized procedure. For example, in EMA or approved in local -- like, when was this product approved? I think one concern I have is some of the products are approved, like many years, may not have the same approval standards among different regions so I think that's something we should consider. So I think it's important to conduct some of the paper assessments about the --

>> Siddharth: I will just add what Wenlei mentioned. We spoke about like, how even Europe there's also like, 27 member states and they have like different procedures. Like, there's the approvals so when you're talking about marketing authorizations for the Europe region, there are some things like, MHRA and you know, like, well informed agencies like, let's say, Swedish MPA and then there's smaller agencies where they follow standards of approvals and different standards of requirements. That's where, while the initiative have been taken and I understand, we're talking about WHO also being like, geared up for the parallel approaches. There's a parallel scientific advice approach which has been taken but honestly speaking, when we're talking at the conventional generic applications, there's not much done in terms of harmonizing these approaches because this discussion also needs to be with regard to the national competing authorities, maybe in the UK or Germany. Or other European member states. If we have to look at these concerns, you know, touch base on the different regions that require different kinds of requirements. Let's talk about the types for that matter. Now, in 2017, FDA came up with a drug guidance that got finalized just last year. And here, this has been looked at where there's no impurity differences. We are okay to be considered as generic applications but this doesn't exist in Europe.

Interestingly, Europe has been the first agency to come up with tons of guidelines for the approvals of biosimilars but even now, synthetic or recumbent, the peptides are considered biosimilars. Unless you look at other authorities, they still ask for extensive, preclinical development and that's where I think my harmonization of global approach is certainly required.

>> Sarah: Thank you so much.

>> Leslie: So in the questions, someone asked if the reference product is different in terms of qualitative or quantitative composition across regions, how can harmonization be achieved? I think the answer is, I don't think that's what we're discussing here. If the reference product is different in terms of qualitative and quantitative compositions, then it's not appropriate reference product across regions with my other panelist agree?

>> Susana: I would like to go back to the points that were made by Wenlei. I think these are great starting points to initiate the discussion among the authorities. What could be used as a criteria? And from Leslie's comment right now, that's an interesting point. I would say that most of the regions that are using these foreign comparators already are addressing most of these questions and starting point might be that the composition would have to be the same, and how do you establish that you're in fact, talking about the same product? I think here an important aspect to keep in mind is that single global development is not a one size fits all kind of approach. In many cases, it might be possible to establish that we're in fact, dealing with the same reference in the different jurisdictions and in this case, the single global development is likely going to be possible if the authorities agree on how. Whereas in other cases, if we're talking about products approved along time ago, where the originators is clearly different, this might not be possible. So I think it's important to establish that this might not be a universal solution. But if it does solve part of the challenge, especially for the newer products I think it's very relevant and good progress that we can make.

>> Sarah: Excellent point in understanding the challenges that lie ahead and maintaining that channel discussion, particularly in areas where there's a maximum benefit to the patients as

well as the protection of the welfare of our patients. With that, I need to transition to over the past day and a half now, we have heard industry suggestion for harmonization of clinical studies across Europe and the United States. This question is directed to all of the panelist but what research areas should FDA invest in and are needed to increase the acceptance alternative approaches of generic drug development in a global market?

>> Leslie: So I'm going to come back to Wenlei's comment and address it in this question. In the paper that we published earlier this year, we looked at food effects and if you look at the data and we have looked at it. About 71 percent of class one drugs show a food effect. You can't just say, if it's a class one drug, it's not going to have a food effect. And we showed in that paper, that basically, just looking at this, we can predict food effects better than any model and simulation that has been published including the papers from the FDA. It's so simple to get them and you have to be better than BDDCS. That says, if you're class two, it will go up, if you're class three, it will go down and class one, it will stay the same and that works about 70 percent of the time. So I think in TERPs of global, from clinical studies in terms of dynamics, in terms of clinical studies with food effects, we need more work on it. Right now, I don't think models and simulation get anywhere close to getting the right information because I don't think we understand food effects. So from a clinical perspective, I think these studies still need to be done.

>> Sarah: We have already talked about the food effect. Any comments on the future of research and the food effect and possible modeling that can actually better predict such impact factors?

>> Wenlei: I want to talk about our food effect versus fed fast studies. We talking about the generic, we think more about the bio equivalent studies and not really food effect studies. I think, I agree with Dr. Benet, for the new drug development, we always need to do the food effect studies but for the fed BE study, we can do this.

>> Sarah: Any other input on the areas? Dr. Blake?

>> Dr. Blake: Yes, Sarah, I think it's important. What I was trying to say in a couple of, albeit small examples I was highlighting. I think we're going to be moving into kind of a,

you know, the complexity of these drugs, it is complex within itself. So I think it needs proactively to identify the questions that might arise and sometimes, even with the example that I gave, around linearity and dose portionalty which is quite an obvious area but sometimes, it isn't adequately addressed and I would also like to take this opportunity to just mention, we have heard about the different European process for improving these drugs and we often say with the project specific guidelines we have here, to the European guidelines, they are also aimed at the NCAs and the member states. And not just part of industry to kind of try to have harmonized position for improving these things. I think they will become critically important going forward but also, with the example I have here, the nasal drug, we do have this kind of referring mechanism within the European system whereby, through CMDH, if there are disagreements, they can be sent to CHMP for harmonized approaches but it's a very valid point and it is this concept. Europe isn't necessarily just one player in the harmonization processes, thank you.

>> Sarah: Thank you so much. Professor Benet.

>> Benet: I want to go back to clinical studies to the presentation. In the beginning, he showed two studies I'm a co author on. The reason we ran these studies, now it's six years since that first study was published was to show that the basic criteria that the innovative product would be equivalent to itself in pharmacokinetics and also, in pharmacodynamics did not hold. That's why we published these studies. Therefore, I'm very pleased to see now, Wenlei talking about the regulatory agency going back and looking at the in vivo characteristics because that's what we have to do. There's no doubt that you can't do kinetics and dynamics on these inhaled products. It's just not going to work. We published it in 2016 and followed it up. That has to be the realistic approach we take. So I always favor the EMA approach. It goes against the basic criteria that the innovator itself.

>> Bill: I think just to say, thank you for all of this. In context of respiratory, it's very essential that FDA, at least with -- that's what I have seen in Wenlei's presentation as well. There are studies that have been done on the modeling side and it's important that you share this information in some sort of repository, that should be available in the generic industry because, you know, give us some guidances on how we, you know, are we going to discover it or do we need to start from another point? I think all of this information is

essential because if you don't have this data, I don't think the generic industries would invest in modeling research because one point you need to realize, it's not even getting the generic. This is a time line. You look into the risk, business benefit ratio as well. The delay or the third or fourth in the market, they would lose that profit. So I think it's so essential, that it's a competitive risk. So in times, it's been seen because of so many complexities and as Dr. Benet also mentioned, you know, like these, what you call, in vitro issues as well. I can show them in my slides. Sorry, the iterations as well. So if there is any data or any guidances or, you know, whatever research, I think it should be shared and I think the investment for the next five years, or let's say, six years, should be developing respiratory models which I believe, because I'm a pulmonologist as well because it's very difficult to build a good, and right, respiratory model because of the complexities involved in the whole lung. So I think you should encourage the generic industries more by sharing the data or you know, sharing the points because, for example, generic industry cannot be doing a modeling evaluation and to develop a clinical plan.

So this is something which I think should be encouraged in one way and definitely there's research focused in this direction.

>> Thank you so much!

>> Amin: I go back to the predictability and so on. Of course, the food effect is something that as a general food effect, it's been addressed by IQ as well as the ICP and in fact, the modeling, I would argue against what professor Benet said, it's doing a very good job in quantifying the level of the effects, not just the direction, this way or that way, but how much of a big issue. But of course, here, what we are discussing as other panel members mentioned, it's not the food effect per se. It's the formulation dependent food effect. How under food effect, one formulation is going to be different than the other one because we're talking about the bioequivalence and in fact, they are not many cases of that. So I would argue that actually asking as a standard requirement all of the time, for the food ebb effect to be done for everything, I think we have to rethink that policy. We have to actually use all of the modeling and simulation help and the information we are getting with the formulation attributes to put in the model, and then come back and say whether there's a reason that in this particular case, we need to look at the

feed effect because we suspect there might be some formulation dependent food effect.

Otherwise, the number of these studies that we may require for the formulation dependent let's say, for instance, ethic differences which I have shown that it happens. You know, that in the case of this, we know it but this is not the norm. Therefore, we have to start using regulatory perspective for justifying what kind of studies are actually really needed and rationalized and therefore, it becomes a little bit of, you know, obviously less subjective. Sometimes, you know, in the quality paper, we mentioned that people come and say that, I am not just happy with that: What do you mean? What will make you happy? Still, saying, we have this, this, this, I would be happy so I think in many of these cases, the modeling can help not just from the side of the generics but also from regulators to justify the request they are having or the other way around to give them a confident factor it may not be needed.

>> Sarah: Excellent question! We can never have enough of this and this does provide evidence based knowledge in this session and this supports patient accessibility by identifying key research needs, to build the translation bridges across our regulatory requirements. With that, we conclude our global session and thank you to all of our excellent panelist and speakers on a great interactive session. We conclude our session and please enjoy the short coffee break. Thank you, everyone!

>> Maria: Thank you Sarah, to all of our panelist. Your input is absolutely invaluable and we greatly appreciate your participation in our workshop, so thank you! To all, good morning, good afternoon, and good evening! Welcome back for day two of this year's generic drug science and research initiative public workshop. We hope you have enjoyed everything so far and are excited for the rest of today. As a reminder, if you have any questions throughout the day, please enter them in the Q & A box indicating who the questions are directed to. We have been answering them live and throughout the day. If you have additional comments or feedback you would lake to provide to FDA, we would kindly request you do so via the comment in the public docket. The docket is open until June 10th. We'll now take our morning coffee break and return promptly at 10:30 a.m. eastern in the United States for session six. Implementing GDUFA science and product development and ANDAs.

>> Welcome back! We're in session 6, implementing GDUFA science in product development and ANDAs. So I'm going to go to our next slide here. I'm director of the therapeutic performance 1, in the office of research standards. This is our disclaimer. The opinions are represented of the speakers and -- I needed to briefly go over our session objectives, is needed to clarify how product clarification test, in vivo studies and other novel methodologies in FDA guidance should be implemented. You should note this is one of the tools for implementing the science that we learn from our research program. To identify challenges and uncertainties, with the data submitted and to clarify approaching to validate novel methodologies and to discuss best practices for the development of suitable test procedures, study designs, model integrated evidence or other matters impacting deficiencies and the number of ANDA review cycles.

Of note, as was mentioned before in yesterday's session, this is the 10th anniversary of our GDUFA research funded program. With that, we are getting to a maturation stage of our science where we're looking to implement some of the information that we have learned in a systematic fashion. So here, we invoke the term of implementation science, loosely defined in the field where we systematically close the gap between what we know and what we do. Often referred to as the know- do gap by identifying and addressing the barriers that slow the uptake of interventions and evidence based practices. So with that, I will introduce our faculty. For my division. YAN and Priyanka are going to be joining us. Our review decision, the office of bioequivalence and we have special guests from industry, Brandon and Meenakshi from India. In our panel, we're going to be joined by Dr. Chong. The presentation is going to start with the discussion around bench to approval regarding the GDUFA research and how we promote complex generics by Dr. Wang and then Dr. Priyanka going to talk about identification of research needs during product development prior to submission and then Xiaoming is going to talk about our research needs to accelerate product specific guidance development and then KE Ren will talk about how we identify the research opportunities from the end of submissions related to bioequivalence for all inhaled drug products and a bit about how our research is implemented during the review. And then Brandon is going to talk about implementing GDUFA science in product development and recommendations from his standpoint in industry and then Dr. Jain is going to talk about this. And

afterwards, the whole faculty will join in for a full panel discussion. With that, on to the talks.

>> Wang: Thank you! It's my pleasure to talk about the role of GDUFA research in promoting complex generics. First, I would like to briefly discuss why, how, and what do I do with the GDUFA research program? What is the purpose of the GDUFA research program? The overall purpose is to promote generic development and facilitate the assessment of generic drugs. How do we conduct research? We have been conducting targeted research projects through internal and external collaborations. Once the project is done, what do we do with research outcomes? We use the knowledge to facilitate development and our revision of product specific guidances. We use the knowledge to help address technical questions received in regulatory increase to facilitate the generic drug development program the and when ANDA is submitted, we use the knowledge to support the ANDA assessment and be final approval. In today's talk, our primary focus is on what we do with the research outcomes by elaborating on the details through a few examples. In the next few slides, I'll briefly discuss how we are using research to support the PSGs. In general, research is helpful throughout the life cycle of PSGs. Before and during the development of new PSGs, and an in- depth analysis of the potential research gaps can be helpful to refine the types of studies, we may recommend to support a BE approach or the kind of research we have to do, prior to being able to develop the product specific guidelines. Once the PSG is posted, we can still identify the research gaps to help support the revisions to types of studies and methods that may be used for a particular bioequivalence approach to further improve the BU recommendation. In addition, the research can also be helpful to facilitate the assessment and in particular, toward a method that may used to conduct the BE studies.

One good example to show how research can be helpful throughout the different life stages of PSG is this system here. In this, we recommend an in vitro, ex vivo combination approach which was not recommended for. This approach was developed based on the understanding of the formulation design as well as potential, in vivo, in vitro drug mechanism. During the drug development, we identified the need for developing a new statistical acceptance criteria for the recommended in vivo, ex vivo study. So we internally collaborated with the modeling division as well as bio stats to address this

scientific gap through a modeling approach. Once it was posted, we realize there's still remaining scientific gaps such as assessment, qualitative of silicon. We have been doing better research to understand the impact of the characteristics on product performance to improve our understanding so we can develop scientifically sound approach to help assess the Q1 sameness of the silicon in a proposed generic. In addition, we also recognize the realtime in vivo testing for this product is challenging. So we have been doing research with the possibility of using the drug testing to replace the need for multiyear, realtime data.

Next, I will switch gears to suggest how the research supports generic drug development. We published our research findings in peer review publications and hope they serve as a valuable resource that the generic company can use to support their generic drug development program. In addition, the approved understanding of complex products enables us to provide more effective feedback to generic applicants while regulatory inquiries such as controlled correspondence and pre-ANDA meeting requests. So in the next two slides, I'm going to give you a few examples to further elaborate on these points.

In this slide, I'm going to give you some publications containing readily acceptable methods. -- published by -- at the University of Michigan. So -- products, through this study, we obtain a better understanding on qualitative sameness of complex, inactive ingredient such as PLJ, as well as gel tan, the second example is about the analyzing the suspension particle size distribution. This was a new method developed by the FDA lab at the office of testing and research. This method was able to accurately measure API particle size without the interference of the inactive ingredient. One thing we recognized about characterizing complex products is the properties of the complex products are often related and are not straightforward to measure or compare. So this is a scientific gap we're trying to identify either during product specific guidance development or through the information we received in the regulatory inquiries and we then try to develop targeted research to help resolve some of this technical difficulties.

The next is about the separation of the PLG polymers when used in a mixture, based on the difference on the ratio. This work was done by (inaudible). So throughout this these three examples, I would like to highlight, we're trying to proactively identify the products, associated with the gaps and

then develop the targeted research to come up with new methods. That may be helpful. But one thing I would like to point out is by no means we are requiring generic companies to follow the exact methods. So how we view these methods, is that they can serve as a potential starting point and companies can adapt what is appropriate based on their program.

I am going on to discuss how the research can help assessment and approval, I would like to give you a couple of examples to show how we have been using research to enable inefficient commune cautions while regulatory inquiries. The example products I'm going to focus on are injectable suspensions with micro particles for short term use. So a couple of years ago, we revised the DPSG for a catalog 1040 acetate, injectable suspension. That revision was done based on our understanding of the critical formulation characteristics and their impacts on product performance and drug release. So ever since then, we have continuously been working in the area of injectable suspensions to identify products or categorize products under different considerations and try to see what our other products that may be able to also have in vitro approach to support bioequivalence. So this was one of the products that we have identified and meanwhile, we also received proposals for several generic applications to develop alternative approaches for establishing the BE of their generic products.

So based on the improved understanding of this through our internal and external research products, our injectable suspensions with particle size in micro range. We were able to agree with the proposed alternative mutual approach, last year, and updated the PSG to ensure timely communications with all generic applicants. Lastly, I'm going to share some insight on how does research support ANDA filing assessment and approval. As discussed before, one area we have been heavily investing is the characterization. So the knowledge we retain from the various projects enables us to develop appropriate acceptance criteria for the Q1 sameness as the recipients to support the end of filing. Research has also been utilized to provide technical support during ANDA assessment to obtain approval. I'm going to give you one example in the next slide.

The example I have here is a complex product and this PSG was the first one in which an in vitro only approach was recommended for supporting bioequivalence of a complex product. Ever since the development of this PSG, FDA has been conducting lots of research to investigate various aspects including the

impact of process parameters on critical quality attributes, how to properly characterize global size distribution, drug distribution of the product, as well as how to determine in vitro drug release from the emulsion, given there's no pendulum method. This long list of publications really highlight the research efforts FDA has investment this drug to have the first generic approval earlier this year. To summarize my talk, first, I hope that through the examples I have shared today you gain some insight on how FDA has been utilizing the GDUFA research program to support projects that are designed to improve the understanding of complex products, issues, which can promote generic drug development and approval. Secondly, new methods developed through the GDUFA research can serve as a starting point to facilitate generic development. Third, we recognize the early identification of specific scientific and regulatory knowledge gaps is critical for generating targeted research outcomes. We have been trying to proactively understand the reference product to determine any under investigated areas that could be very critical for generic development so we can develop targeted research accordingly.

We have also been accumulated feedback on practical challenges faced by generic applicants during drug development, with regulatory inquiries, therefore, it's very important for generic applicants to communicate with us about your technical difficulties in a timely manner. With that, I would like to thank for your attention and I'll be happy to address any questions, comments you may have during the panel discussion.

>> Good morning, everyone. I'm Priyanka, an acting team lead in the standards of generic drugs and following the presentation today, I am going to talk about how do we identify research needs during the process. Specifically, how early identification of research needs can ultimately help us to achieve our mutual objective of getting more high quality generic products available on the market.

This presentation reflects my views and should not be construed to represent FDA's views or policies. The goal of the presentation is to discuss how GDUFA research has contributed to the development of BE recommendations and I'm OO going to use topical dermatology dosage forms as an example and talk about how the identification of research challenges and needs prior to the submission of an ANDA can be helpful towards the ultimate success of a product development program. I'm going to use this as an example. So where are we at with these topical dermatology products? Historically for these low

acting dosage forms, we have recommended declarative, BE studies -- however, we have recommended efficient characterization based approaches.

The development of these efficient category, in the science research program and I'm going to show you a very very small snapshot. In this example, we will look at these creams and gels. These products are known to be BE based on the clinical studies and we did micro structure or Q3 characterization of these drug products. What we saw was, when the Q3 of the products were similar, the performance was similar and it was distinctive different when products of Q3 is different.

We saw this not only for this product but a whole host of drug products which ultimately led to the development of efficient characterization based approaches. Now, within the scope of these efficient characterization based approaches, we have what we refer to as a modular and scalable approach to BE evaluation where we are trying to develop a generic product that is very very closely matched to the reference product such that, the performance of this generic product can be expected to be similar to what we would expect across different batches of the reference product itself. And we do this by recommending sameness in formulation, there's the assessment of drug release and as the complexity of the formulation increases as we go from single base to emulsion, we also recommend IVPT or another bio relevant assay and in some limited instance where there could be a potential site of action, we may also recommend a PK study.

Each of the guidance shows the complexity of the dosage form as well as the site and mechanism of the specific drug product. This is a topical gel that has micro particles or micro sponges suspended in the gel. When we look at them, they appear to be porous structures and they may be in the surface or within the pours and we can read more about it within the research report or in the presentation from SBI last year. One key conversation that we identified is the location of the drug within these micro particles, either on the surface or within the core of the micro particles has the potential to influence the drug release from these micro particles and ultimately, the bio availability from these drug products.

So why for a single topical gel, our research shows that the sameness of the inactive ingredient components and quantitative composition, may be sufficient. For these topical gels contains micro particles, we may need to consider

additional studies. We may need to understand the materials that constitute these particles. We may need to assess the micro particles within the drug product and the morphology, the surface area, the drug loading and distribution, and localization of the drug, as well as the physical state of the drug on these micro particles to be able to ultimately understand what factors may influence drug release and bio availability.

Overall goal being, we really need additional research to understand the complexity, the additional complexity that is associated with these topical gels containing micro particles to be able to efficiently development these approaches for such products. The second example that I have for you today is for topical emulsions. Like I said on the previous slide, for these topical emulsions, as we get in these systems, we typically believe that another bio relevant assay may be needed to be able to mitigate all potential failure modes for these complex forms.

Now, I have the contents listed for this product. We have often discussed that for these multi- phased systems, if the drug, if the API which appears to be hydrophilic in this example is largely located within the base of the formulation, then do we really need the IVPT study? Well, we did some research led by the division of quantitative methods and modeling and in this small demonstration that I have on the slide here, we saw that as the formulation evaporates, the percentage dose of the drug in the continuous phase and this phase changes over time.

We know that the relative contribution of the drug in the oil phase and the aqueous phase, may influence the bio availability so it is critical to utilize a study such as an NVPT to be able to adequately mitigate all potential modes for a product which is a topical emulsion. While we understand these things, we still think it's an important component of a lot of characterization based approaches that has the reference product is an emulsion and specifically for this case here, we had an additional challenge. This drug has the potential to medicalize in the skin. So now, we need to consider do we monitor this drug in the receptor solution? Do we monitor it in the receptor solution? And how do we identify which analyte for this approach. So again, here's an example where we think, if you are interested in developing such a product, or similar products, only engagement and discussion between the industry and the agency may be beneficial towards the overall goals of

the product development program.

The last example I have is topical foams. Historically, foams may qualify for a waiver of in vivo balance study requirements, and in those situations, we would say characterization tests but corticoid studies, we may have clinical end point studies but what we need to remember and I'm just going to show you two forms with the respective compositions and what we see here is some of the inactive ingredients is complex. So coconut oil among other components. What we need to consider is we are still at a stage where we are trying to understand the micro structure of these foams. We're trying to understand how the inactive ingredient the impact the structure and what the element Q3 properties may look like. And lastly, do we use the collapse form or the form as dispensed from container project system? The point being, we still need to do additional research to be able to develop efficient characterization based approach for these products and in the mean time, if you're interested in developing such products, only engagement with the industry may be beneficial to ultimately move the products forward. In summary, I hope was able to communicate with you, that like a lot of products we discuss today, these topical dermatology products have different forms. We have identified characterization within the scope of the GDUFA research program, however, there are complex questions and identifying these research needs during the pre- ANDA process and only engagement between industry and the agency may be able to help us to develop a strategy that can then be utilized to facilitate generic drug development. I would like to acknowledge and thank our entire team as our research collaborators and all of you for your contribution to this research program. And I look forward to your questions during the Q & A.

>> Good morning! I'm within the office of testing and research in OPQ. In the next few minutes, I will continue the discussion on the GDUFA research and focus more on the translation to support the development of product specific guidances. As the title indicates, the scope to complex products. They are challenging to develop and hence more likely to need additional research. In it talk, I will provide an overview as well as the product specific guidance program. Share some of the GDUFA research examples and specifically how they have helped to fill in the gaps in the scientific understanding and support the development of PSG as well as generic review.

This will soon be authorized again under GDUFA three. In addition to user fees and time lines, this program allocates resources to the FDA to have research to facilitate the drug development and review. For example, since 2013, FDA has awarded 188 research grants, led by FDA staff. This research facilitated the development of new tools and methods which helped the FDA and industry to evaluate the generic drug equivalence. A key outcome of this GDUFA research is to enable more efficient development and assessment of generic drugs as well as improved resources for the development of PSG recommendations. A key aim is to disseminate the research findings to improve the general understanding of this product and to aid in the generic industry in their product development program. Therefore, results from this research are shared through scientific meetings as well as peer review, scientific publications.

The product specific guidance program that began in 2007 aims at facilitating the development and approval of safe, effective and high quality generic product while providing FDA's thinking in demonstrating the approach to the specific reference listed in the product. PSGs are published on a quarterly basis on the PSG website which also includes information related to upcoming new and revised PSGs for complex generic drug products. One of the key outcomes of the GDUFA research is the development of this PSG. It is important to note that PSG is FDA's current thinking and the applicant can propose alternative approaches deviating from those recommended but they should provide justification of the proposed approach and including the data and appropriate references. In addition, as a negotiated in GDUFA 2, the FDA has agreed on priorities and goal days on the development of these PSGs. All of this information can be found in the link below to the PSG website.

On average, there's close to 100NDA approved a year that could warrant the development of a PSG. Of those newly approved NDAs, about 25 percent are complex product as defined in the GDUFA 2 letter. This has dosage information and forms and can meet more than one definition of complexity, such as complex active ingredient, route of delivery or complex dosage forms. To are shown on this slide. The one on the left is a biodegradable PLGA implant of the medical which provides ocular pressure reduction in patients with open angle GLA coma or ocular hypertension, upon administration, the product is designed to provide sustained drug delivery for several months,

modulated by this. The complexity of this product include complex dosage forms, as it is an implant with complex recipients and complex route delivery, for example, this is through intracameral delivery.

This also includes the application device used to deliver the implant. The example on the right is an RNA indicated for the treatment of a rare disease condition called primary hyper-- type 1. Nucleotides like this are considered complex drug substances as they present unique analytical challenges as well as impurities. These two examples highlight the challenges including the need to understand the design of the drug product and come up with the proper techniques or products to characterize it to show the equivalence. This commonly recommends a type of study or property to be measured.

It is up to the generic applicant to select, develop, and justify the proposed approach. This includes justification of the development methods and the evaluation criteria used to compare the generic and reference listed drug products. As I will show in the next slide as an example, the GDUFA research can help the FDA and its industry to develop and stay informed of new analytical tool for assessing a specific product or class of products. This is important because some of the properties of the complex products are inter related and not straightforward to measure or compare. The GDUFA research aims at reducing the potential scientific and regulatory hurdles by providing more insight in the properties and approaches and providing the industry with a starting point to the generic drug development.

Extensive research has been conducted in this area both internally and externally to address the key questions facing this class of products. In the specific case, the products are complex in terms of both formulation, which is an emulsion and the rate of delivery which is locally on the ocular surface. To a notable products in this class, includes cyclosporine. Both of these drugs, for decades are without a generic. GDUFA research played a critical role in the understanding of the product properties, development of the proper analytical methods and helped both the development of the PSG as well as the ANDA review which led to the final approval of the first generic for both. For example, several physical chemical properties such as the distribution, viscosity, drug distribution and release have been identified as having a greater influence on the product quality and influence and may be impacted and may need careful examination to ensure product

equivalence.

Further research was conducted to have best method practices and evaluation criteria to support the assessment of these properties. A few research publications are listed below for your information. As you can see, this has a significant impact on reviewing NDAs and also a valuable resource for the generic industry use. Here, we have highlighted a few examples of recent accomplishments both NPS and in the approvals for a few GDUFA research priority areas. This includes the priority of the first generic Hydrocodone formulation. The first lipsome injection, and the first injectable suspension and first generic ophthalmic emulsion. Ultimately, GDUFA research helped to facilitate the industry generic development and the FDA's assessments. All of these findings can be found on the GDUFA FDA website. Before ending my talk, I want to share my thoughts about challenges and opportunities in future product specific guidance development for complex products.

As we have seen with some recent approvals, complexities vary greatly between products and across can disciplinary areas and can benefit with a close collaboration between teams. The use of new materials, technologies and processes in these NDAs highlight the potential gaps and the need for new and reliable methods which needs new research and innovation. Furthermore, in GDUFA 3, the new goal dates on the development of complex products may pose a potential time constraint especially if additional GDUFA research is needed. So early engagement of research and review will be crucial. Lastly, taking a life cycle approach towards the development of the generic necessitate better communication and collaboration across teams and in the industry. To summarize product specific guidance program provides FDA's current thinking on the type of studies and information to support the development and approval of safe, effective, and high quality generic drug products and GDUFA research plays a critical role in the generation of the evidence and knowledge and supports the timely development of the PSGs. I want to thank a few people who helped me put together these slides. Thank you for your time and attention.

>> Thank you for the introduction. My name is Ren. I am in the division of bio equivalent 3, office of bioequivalence within ODD. Today, I'm speaking about identification of research opportunities for ANDA submission related to bioequivalence for orally inhaled drug products. Here is my outline. First, overview of FDA recommendation on BE assessment for orally inhaled drug products, OIDPs. Next,

alternative BE approach to comparative clinical end BE studies. For solution based middle dose inhaler MDI. During our ANDA evaluation, we received some applications, used alternative BE approach for suspension based MDI. We will discuss additional considerations and the further research for using this approach for the suspension based MDIs. I will share additional consideration for the formulation. Lastly, I will provide a summary. Developing generic -- is challenging because of the multiple factors that can inference drug delivered to the site of action. For example, the interaction between the formulation and the delivered device can inference how the aerosol performs, which can impact regional deposition, subsequently, the solution of the deposited drug. The patient and the device, the interaction, which can consider the complexity of using the drug product. Can impact those of demonstration which also inference the regional deposition. Also factoring together, can inference overall absorption of the drug, with the deposited at the site of action. To address challenges for locally acting OIDPs.

The current method we use is the weight of evidence approach. It includes in vitro study, in vivo study, comparative, clinical and BE studies. Formation sameness and the device compared with reference product. With this approach, each of the four components needs to meet the bioequivalence material. There are so many challenges surrounding clinical studies. In the weight of evidence approach, to make it difficult to establish the bioequivalence for the middle dose inhaler and dry product inhaler such as higher availability and lower sensitivity for evaluation of formulation difference. Longer study duration and the more costly than other type of bioequivalence study. Therefore, alternative bioequivalence approach can be used to address these challenges.

As you can see, the local delivery of API is complex. Multiple step process with each step impacts the next. The alternative approach for OIDPs should consider all of those steps. Alternative approach to the comparative clinical and point study has been published in several PSD solution based MDI including the middle dose inhaler. As recommended in the PSG, if our generic sameness and the device similarity to the reference MDI, additional supportive study may provide a foundation to help ensure the equivalence at the site of action.

This study, includes the following characterization of emitted spray. Velocity profile and the evaporation rates that

can help to achieve and understand the drop size and evaporation process of the formulation made from the device. This is the duration of the residual drug particle size. Another supportive study is to use more predictive APSD testing by using representative through model and the breathing profile. This can help to capture and understand the impact of patient availability under the drug deposition. In vitro dissolution study can help to understand how API drug particle dissolved at the site of action for absorption, once deposited within the lung, quantitative method and modeling such as physiological based PK, computation fluid can be utilize today provide data to help bridge the gap between the individual product performance, and the original drug deposition. Alternative study can be considered to understand how the PK study can correlate to local deposition.

So when considering alternatives bioequivalence approach for suspension based MDI, the difference in drug delivery process compares with the based MDI, particularly the effects of suspended API particles in the formation should be considered. For example, it may include understanding the surface level interaction that could impact downstream process critical for the original drug delivery such as the electrostatic force, to change the -- over time through this. The surface API particle may impact the stability of the suspension. Interaction with the API contributed for the foundation stability which may need to lead to a difference in PSD of dry particles. To address these factors, characterization of suspension based MDI, may need to be considered. So as our example in addition to the study discussed earlier for the solution based MDI products. Characterization of the effect of suspended API particle and the interaction with formulation under the drug delivery process could also be included in the alternative bioequivalence approach for suspension based MDIs.

Please keep in mind this is important that alternative approaches include a study, adequately to address how these suspended particles impact each aspect of drug delivery process. This highly encourages that the applicant submit their proposal for the alternative BE approach or suspension based MDI through pre- ANDA meeting request.

Here is some general considerations for alternative BE approach for OIDPs. Approach should address sameness of delivery at the site of action. Approach should be scientifically justified with our comprehensive data and

explanation. Due to the complexity of many different factors that can affect the generic drug performance. Critical key attributes for suspension based MDI may be product specific. It's important to understand key quality attributes of your generic product comparing to the reference product. That is an inference on the in vivo study. Next, we'll discuss the formulation sameness. Even though there's no new requirement for the Q1 and Q2 sameness for a certain requirement, specific BE approach may be recommended in product based guidance such as, oral suspension locally acting drugs and or IDPs. Along the Q2 application with no regulatory requirement may be submitted to FDA for OIDPs. However, sufficient data and information can lead to justify the impact of formulation difference by equivalence and safety.

The first long Q2 data for the NDI product is proved this year in March. If the applicant wants to develop their products, not Q2 as the reference product, recent studies should be submitted to demonstrate the formulation difference does not affect the product performance in the submission. For example, evaluate the impact of different amounts of the proposed excipient, testing of multiple drug- to excipient ratio that encompass combination below and above the ratio in proposed formulation, on drug performance. Please keep in mind that the level may or may not impact the product performance. This could be considered on a case by case basis.

In summary, OIDPs are complex drug device combination product with multiple factors contributing to their performance. The type of study includes as part of alternative BE approach with the clinical and point study where the product specific. As different in dosage form and formulation where given to a different area of an uncertainty.

Applicants, I highly encourage to submit a pre- ANDA product development meeting request. And seeking agency feedback on the proposal. The approach should be scientifically justified without comprehensive significant and -- body of data. I would like to thank my members listed here for helping me develop this presentation. Thank you for your attention. M.

>> Hello, my name is Brandon Wood and I'm an associate director at Teva pharmaceuticals. I have been a regulatory professional for over ten years and specialize in complex generic products including peptides, iron colloids, long acting injecting and

combination drug products. The title of my presentation is implementing GDUFA science and product development in ANDAs, realizations and recommendations.

Here is our standard disclaimer slide. In terms of presentation content, we'll start with the industry perspective on the GDUFA science and research program. Then we'll discuss realizations and recommendations for complex mixtures and peptides, complex injectables, formulations, nano materials, drug device combination products and long acting injectables and then wrap up.

I would like to start, in summary, the GDUFA established a science and research program at FDA that is implemented through extensive intramural and extramural research collaborations. The program supports the development of innovative methodologies and be more efficient tools to help establish drug equivalent studies and be support the development of safe, effective and high quality generic products for the American public. This research particularly important for certain pharmaceutical, that is harder to develop as generics. Complex products have fewer generics or none at all and in the absence of market competition among these, these medicine KS be so expensive that the patients that use them may not be able to afford them.

From the industry perspective, it's clear the realization of these programs, scientific articles, posters, characterization techniques, BE are vital for these complex generic products. There's certainly alignment on the topics and initiative that can greatly benefit from additional research. And also the program will be fundamental in addressing technical uncertainties and challenges that continue to arise for these types thus, enabling timely approvals. Now, we'll move to realization and recommendations, our first product time is complex mixtures and peptides. To start with the overview on the fiscal year 2021, research efforts continued in the development of advanced analytical methods for the evaluation and characterization of complex active pharmaceutical ingredients including complex mixtures, nucleotides, peptides, and synthetic polymers. Within Teva, characterization with complex, using advanced analytical methods are essential in supporting the pharmaceutical equivalence and linking product attributes to safety, quality, and clinical performance.

Thereby, facilitating the generic drug development and

approval process. Moving on to the realizations. In the fiscal year 2021, FDA issued a final guidance, ANDA for these drug products that are the R DNA origin in May of 2021, issued two new PSGs related to complex mixtures and peptide products, published 1 new article and facilitated two poster as well as six presentations. I would like to take a second to make two notes. All overviews and realizations in this presentation were taken from the fiscal year 2021, GDUFA annual report and I would like to note THAT realization here and presented throughout this presentation is in addition to the new continued and completed grants and contracts as well as active FDA research.

So while acknowledging the great realizations for these product types, I would also like to explain some challenges, examples and provide a recommendation that may be useful. A challenge with respect to mixtures and peptides is new impurities but at a higher concentration are handled on the case by case basis, using the totality of evidence. Including in vitro immunogenicity studies which are prevalent, but there's limited guidance for study design considerations, and expectations. Just to provide an example, only after multiple review cycles for one product that we learned of a minimal dilution test level. This is not discussed in guidance or creating the DNA feedback and is previously unknown requirement impacted the completed and the planned studies.

As a recommendation, from a public domain standpoint, if FDA could develop multiple validated methods for these the agency finds acceptable, it would likely reduce the number of deficiencies in CRLs. Additional specificity and guidance would reduce the number of review cycles. So moving on for realization and recommendation, our next product type is for complex injectables, formulation and nano materials. In fiscal year 2021, injectables, formulations and nano materials focused on the following aspects. One, the development of novel, in vitro drug test release methods, two, the evaluation of analytical methods for characterizing complex injectables and three, use of the model to evaluate target site bio site -- of materials. And four, investigate the relationships between physical, chemical features of these and product toxicity. From a Teva perspective, characterization is important to demonstrate these sameness, we review the PSGs, articles, posters issued by the agency to ensure there's a common understanding of the techniques and expectations for advanced characterization tests. In fiscal year 2021, they have reviewed ones, published four articles, facilitated 7 posters

and 11 presentations for these product types.

Moving on to challenges and examples and recommendations for complex injectables formulation. As a challenge, I would like to note, there's no methods established by FDA. What we see is deficiencies in CLRs and how the insufficiency, only during the review process is FDA asking industry to following a specific methodology. We would like to note that the requirements are changing and the in vitro -- are debatable. To provide the example for one product, data was provided for a physical characterization. The samples were finalized but only after multiple review cycles did they request it be done on frozen examples. This was not previously discussed in guidance or FDA feedback and could have been avoided if the preference was known.

So as a recommendation, conduct the research to publish publicly available and analytical methods with sufficient level of details in vitro characterization or developed guidance that communicates FDA designs with these formulation asks be nano materials and we would recommend that the agency facilitate further evaluations of the in vitro parameters clinically meaningful.

Next for realization and recommendations, we can move on to drug device combination products. In the fiscal year 2021, FDA continued to perform research related to the impact of identified user interface differences on the therapeutic equivalence on these combination drug products or DDCPs and their reference to drugs. In the absence of a final guidance, Teva has utilized numerous meetings to work with the agency to develop acceptable, comparative use, human factor study designs to justify other differences present in the final user interface.

Where realization in fiscal year 2021, FDA issued one new PSG that is directly impacted by the research in this area and facilitated nine presentations related to the drug device combination products. Moving on to challenges, example and recommendations. One significant challenge for drug device combination products is there's no available guidance that represents FDA's current thinking and how to calculate a non inferiority margin to employ a CUHFS study. I would like to note, there's a discussion on the non inferiority margins in the draft guidance industry, comparative analysis for a drug device combination product submitted in ANDA January 2017. However, for recent feedback draft guidance does not represent

FDA's current thinking.

For one DDCP as an example, we submitted a controlled correspondence requesting feedback on our proposed CUHFS protocol. FDA responded strongly recommending a pre- ANDA meeting and we took the advice and asked for the request. Later, the meeting was held. However, it was recommended to revise the protocol and submit another controlled correspondence. In total, it took fourteen months to get meaningful feedback and I think the agency would agree that it is not conducive time line for generic product development. So as a recommendation, regulatory science and research regarding acceptable study designs, non inferiority margins that can be employed in a CUHFS including workshops, training, and focus groups would be beneficial to FDA and the industry. Research in this area could facilitate a common ground whereby, other differences between test and RLD combination products could be effectively managed and not preclude approval BLT, via the 505 pathway. I would like to know, there's another session on this comparative use human factor studies.

Our final realizations and recommendations are related to the long acting injectable products. As an overview in the fiscal year, 2021, aim to one, develop MU tools for characterizing the complex polymeric excipients and, two, better understand the impact of variation in raw materials, on formation characteristics and drug release and three, explore the new in vitro drug release testing, methods to have better clinical relevance and investigate advance imaging tools and five, develop new modeling tools to support the alternative approaches. Teva has utilized numerous pre- ANDA meetings as an alternative bioequivalence approach R for long active injectable products. For the realization in the 2021, FDA released 4 new SPGs, published 15 articles, facilitated 12 posters and 5 presentations for long acting injectable products. So describe the challenges along with the example and recommendation for long acting injectable products, I would like to note that FDA has indicated an interest in seeing modeling and analysis plans in terms of model- based approaches for bioequivalence assessment if proposed as part of the pre- ANDA submissions to submit occurrence prior to execution. It has been highlighted that information requests are common for these types of pre- ANDA meetings and take time away from the assessment clock. Model integrated evidence can have a meaningful impact on reducing the duration but this specific expectation is unknown. Teva has now submitted multiple

reviews. Without an understanding of the specific elements that FDA would like to review for modeling and analysis plans, these pre- ANDA meeting packages often have 75 plus attachments, meaning, we provide everything from scripts to individual data sets, really, it's unknown to know if package is useful for the agency review or whether we're providing too much.

So as a recommendation, it would be beneficial to both industry and FDA if there was a mutual understanding of the information to be submitted in such pre- ANDA meetings to make the most of the meetings and set a strong foundation for the alternative BE data. Additionally, we would like to recommend providing guidance for the specific model integrated evidence, specific approaches, designs and templates for submitting the information in a pre- ANDA meeting or in an ANDA. To wrap up my parting thoughts. The agency's output from the GDUFA science and research program will inevitably enable a stronger environment for the complex generic product development. Continue feedback and industry agency collaboration will streamline the utility of the research performed and focus should be put on ensuring that the research performed is compatible, useful and pre producible for generic applicants to incorporate in the developed programs. Detail is key!

Now to close with a quote by Winston Churchill I thought is very appropriate. Out of intense complexities, intense simplicities emerge. Thank you!

>> Good evening, everyone! It is my pleasure to be a part of this session 6, implementing GDUFA science and product development in ANDA and share some insights from the industry perspective. Let me share with you the disclaimer first. This presentation is based on publicly available information. And the views presented are the views of the presenter and not those of these companies. The agenda for this is the reflections for GDUFA science and research, challenges and opportunities for some of complex projects and going forward for implementing the GDUFA science early in development. In this slide, we will talk about the reflections of GDUFA science and research.

Several pharmaceutical products are harder to develop as generics and few have generics at all. In the absence of market competition among generic alternatives, these can be so

expensive to patients who may not be able to afford them. The outcomes for GDUFA research, expands the understanding of these complex products and often contribute to the development or advance methods to characterize product quality and performance. The GDUFA research outcomes also prepare FDA to assist in the ANDA references complex products which ultimately improve patient access to complex generics that are presumed to be unvisible to develop even just a few years ago.

In front of you are some of the reflections of GDUFA science and research already conducted in 2021 for complex injectable, formulations and nano materials, complex mixtures and peptide products, immunogenicity risk assessment and ophthalmic products. Based on these research outcomes, the FDA approval for this was received.

As part of FDA's commitment in expanding your collaboration and commitment to industry, the center for research on complex generics was established to enhance how generic industry stakeholders and team work together to over come challenges impacting patient access to high quality, safe and effective generic products. Coming to the next topic, sameness and immunogenicity assessment.

These are short, synthetically derived RNA and DNA strands that influence gene. These are small molecules regulated as drugs by CTR and follow a regulatory pathway. This exist like (inaudible). There are additional challenges for the drug development and no FDA guideline that address the quality aspects and expectations. Most are solutions for injections and BE may be considered self- evident, hence, bio availability is possible, provided API sameness is established and testing R & D is comparable. Three batches of the test product and the RLD is required for the API comparison and the sameness study. And impurity characterization by alternative methods is required as most impurities exist as mixtures of closely related molecules and many impurities score -- to be the active ingredient. It is also required to include information to justify that any impurity difference in the generic do not give rise to unknown differences in immunogenicity or toxicity. However, this lack of clarity and we're required to contact FDA for further questions.

To address these challenges, FDA is actively working on characterization of this to support drug equivalence. FDA has developed this for sequence characterization and impurity analysis of synthetic and product related impurities and also

issued a product specific guidance for these injections in February of 2022.

FDA is also planning to publish 6 product specific guidances in the near future. FDA recommend that they use appropriated validated orthogonal methods to have a side by side comparison. The primary sequence can be controlled through each elongation cycle in the synthesis due to the -- on the linkage using the synthetic different types. The expectation is to measure this at each linkage following each elongation cycle using appropriate methods. So the approach for showing this, and -- for the mechanism analysis should be appropriately as defined. Hence, we request FDA to do further research on analytical methods for comparing the test product and RLD and also, sequencing and impurity identification and quantification by HRMS requires advance software. So the current software is not validated and can be used for research purpose only. So we would like them to collaborate with the software providers and recommend some specific software.

Further, there are no general guidances available for reporting identification thresholds for this. Supporting the threshold directly impacts the analytical development, therefore, it would be good for promoting thresholds. As for this, generic applicants are advised to conduct FDA for questions related to immunogenicity and impurities. So in general, this is relatively small, contain fewer isotopes than the larger counter parts and less likely to generate immunogenicity. DNA is generally thought to be relatively non immuno genic. This shows a low potential for this induced immunogenicity based on the route of administration and the ANDA relies on the FDA finding that the previously approved drug is safe and effective. So we believe the potential is slow, hence, we request FDA to do active research and provide guidance on how this genetic nucleotides should be addressed and what studies should be performed if needed.

If FDA can provide guidance on clear risk assessment, that we can follow and if there are any in silico tools available for assessing the potential for this. Coming to the next topic on complex products. API sameness study is for these complex. There's different expectations for the review as well as for different products. While on one hand, the expectation is to demonstrate the API sameness by a minimal that manipulation of intact RLD. The drug product manufacturing process, for example, sterilization can have impact on the API properties, with believe that this can show an unpure quality in drug manufacturing process while physical, chemical process,

sameness study and RLD should be sufficient as patient is receiving the final drug product. So we request FDA to do some more research in this direction and if they can work on some specific case studies and provide clear directions in product specific guidances or provide general guidance for the sameness study. Also, there are no guidances on the acceptance criteria for demonstration of sameness for complex products. If FDA can explore and provide guidance, how to set the acceptance criteria for demonstration of sameness for complex products would be very beneficial.

There are no guidance on the extent of method of validation and qualification for the characterization methods which are used for the sameness study and comparability testing. Can FDA publish the guidance on the extent for the different types of methods that are advance techniques. Some of the techniques are listed here. Coming to the next topic for ophthalmic products. So in financially 2021, efforts address challenges in three areas. Development of in vitro release methods that more closely resemble in vivo conditions. Identification and characterization of critical physical, chemical properties of complex ophthalmic products, advancement of modeling to investigate the impact of the formulation properties on ocular PK/PD.

A new model was developed employing the filtration. So the method was also published in the journal of control release. Also, FDA is actively working in these areas in this area here. With adaptive population method is useful for industry, it may not be suitable for all 'ol thalamic products and industry may not have access to these techniques so the development of in vivo test methods that move closely resemble in vivo, these conditions may not be used. It's not clear to what extent -- and should the discriminatory -- critical attributes so we would like to do more research on other methods, like, these listed here. That are relevant for the in vitro release and to do more research to identify critical attributes to show the discriminatory capability of IVR method.

Coming to the next topic on impurities, observed in generic drug products based on levels. They are not available in the market and are close to expire and not available. Would these scenarios delay the access to the medicines to the patient? Can it be accepting this based on the ASAP, small data for small molecules at the time of submission and supplementing the data with this during the review process.

Can we accept the justification based on Europe, Canada or any other approved genetic products? We would like, FDA to make a process for FDA approval with the use of the EUSRLD data with the impurities and characterization studies.

To request the update data base of the outcome and make it available to the industry. Provide access to the literature research articles and leveraging product development meeting and controlled correspondence early in the development would be very beneficial and if FDA could provide specific inputs and directions during these meeting would be helpful. Adequacy of test and methods is normally a review issue. This should be aligned during product development meetings to ensure the smooth process and opportunity for realtime communications with FDA would be very beneficial.

These are some of the differences used for this presentation. Lastly, I would like to thank all of my colleagues who have supported me in every step.

>> Luke: All right. So we're ready for our panel. Let's have all of the panelist join us. That was a fantastic set of talks! I must say, you guys hit it on the nose. There's a lot of good topics being brought up. And as I mentioned in my introduction and as we have discussed during our discussion sessions, a lot of what we have been presenting could be discussed in the context of implementation science. That science suggests that this, that the research and science is ready for implementation and there are certain sciences that are not yet ripe for implementation or we're still working on it, like I pointed out, in one of the talks about comparative use human factor studies. That's still a developing science. If you Google it, there are hardly any references or papers about like the end or what -- what the population you need to do a comparison for certain types of devices, et cetera. And the same for all of the nucleotides. Those are recently approved in the big framework of all of the drug products that FDA has approved. So this is just starting off the discussion, I think, we have some really good questions coming in. And I wanted to say, first of all, before we go in discussion, I want to introduce Bill joining us! Hi, Bill!

Bill is joining us from the office of clinical safety -- OSC.

>> Bill: Office of safety and clinical evaluation.

>> And OGD. Bill is the director there. We also have Utpal. They do the hard work of all of the things coming and he brings in lots of great years of clinical context.

Let's get to the questions. We have many topics for many different prototypes. What in your opinion of the discussion points will provide an immediate benefit to industry? Again, keep in mind the framework of the implementation science we're bringing up. Brandon?

>> Brandon: Yes, sure. I'm happy to answer that one. So I think two topics specifically that don't have FDA's current thinking documented and guidance or otherwise, really related to the comparative studies and you had allude today it but comparative use factor studies. I think understanding the implementation science and you know, very specific details may not be development at the moment but we're looking for general recommendations and current thinking on study designs because for immunogenicity, if we have general recommendations or you know, overall thoughts, this can avoid pitfalls when later in the review process, especially considering that the testing is done in the beginning and end of shelf life. So you get in a scramble if there's a specific question on the review process. And then, also for a comparative use manufacturing study, I think, really again, general recommendations. Understanding that it's a newer area it would be very helpful to industry and then in this sense, because it is a newer topic, I think what general recommendations could provide is a leg up in terms of taking proposed study designs to pre- ANDA meetings and have a more robust discussion on an acceptable study design and maybe, not inferiority calculation. Just more discussion on the product development meetings so we can walk away and have a more streamlined approach to address other differences identified in a final user interface but just two topics where I think, even general recommendations understanding that it's a newer area. That there's still thinking and evolving thinking, happening for immunogenicity and comparative use studies. General recommendations could help ensure we're headed in the right direction and ultimately reduce the number of review cycles for these drugs.

>> Luke: Great! Bill, do you have a response on the studies? Any comment there?

>> Bill: No major comments on that. I appreciate the perspective that was raised here. Having a little bit of a

framework can be useful. Acknowledging when we're looking at product specific factors and things to be considered and like, what is the context of use and how complex the device is. I don't want to comment too much because I understand there's a whole separate session focused on combination products and I suspect, there's a little bit more in- depth discussion there. But your points are well taken, Brandon and I think there's some things for us to think about.

They are both on this comparative immunogenicity, like you said, some general framework for you guys to think about and work around, that may be useful. So I appreciate these comments.

>> Luke: Thank you, Bill! Do you have any questions? It my understanding is they are usually protected from the immunogenicity aspect because they're things that wrap around them when you deliver them. Like lipids or carbohydrates to protect them yourself. In that case, how much of the immunogenicity is related to it, versus the recipients involved? Your thoughts.

>> Wang: Thank you! I think the peptide and immunogenicity risk assessment is a new area for generic. Because generics are like new drugs, everything from a comparative standpoint. So here, like I mentioned, we definitely appreciate your feedback on the challenges, especially with the method validation, development, for assessing the immunogenicity but at the same time, I think we're also trying to really understand when such a study is essential. So I think that is critical in really understanding and by looking at the product and characterizing the product and have internal discussion to understand the different perspective as well, when to know when you can do the product development. Then what are the things we look at first.

>> Luke: My understanding is that some of the immunogenicity issues that have come up, are related to the presence of impurities that resulted in the reactions to the API. Things like the presence of metal ions, et cetera, that were not supposed to be there. I think that's the case of this, in the European case. I did want to go on to our next panelist. What topics provide an immediate benefit to the industry?

>> Meenakshi: So we briefly discussed the no generic products that are already approved, so still, talking about the immunogenicity assessment. I think directly implying the

peptide guidance or biosimilars for immunogenicity. We may look at the approved products, like if the FDA can go through the post marketing reports, whether the immunogenicity is really a concern for these nucleotides. In general, there's reported examples that they have low immunogenicity potential so maybe more research in this direction can be helpful for the industry. And of course, the characterization methods which are very advanced techniques and due to very high impurity, possible products where it's closely related to the API so more research in that direction and more research on the diasteric combination which we have already expanded and my presentation would be helpful. Apart from that, inventory release methods for some of the, maybe, ophthalmic products or long injectabling or such kind of products are also helpful for the industry.

>> Luke: I wanted to thank you for your thoughtful presentation and taking time out to basically make utility for the topic of the session to identify the gaps and this is the whole purpose of the workshop, overall is to see what kind of gaps exist in our current research environment and your carefully thought out proposal is very great. Did you want to comment on what Meenakshi had said?

>> Utpal: Thank you, and excellent presentation. I enjoyed the session this morning. I had one thought when we talk about implementation science and some of the comments from our industry colleagues this morning. That is, I think what we heard is that, you know, in some cases, I think we're looking for just a general framework on how to proceed in a certain area and then I noticed that there's some specific areas where maybe there's a need for additional material in terms of things like acceptance criteria. So one question that comes to my mind is how much detail is too much? Because while we want to provide a very important framework for the industry to follow, if we get into granular and specific, does that stifle innovation? Does that make us too restrictive in terms of how we evaluate these products?

One thought that comes to me mind or question for industry will be what is sort of your general thinking about when is -- well, at what point do we want to say, okay, this is maybe too much detail or the expectations are too much from the agency and that's stifling our development? That's a question in my mind.

>> Luke: Utpal: That's a fantastic comment! It goes to the

heart of some of the things that Brandon was speaking, I was thinking the same. Brandon, you're asking for more specifics but sometimes you have to be careful what you ask for, right? So that context, where is the magic space where you get just the information to move forward with your development program but not so restrictive that FDA is going to either refuse to file or not approve it because you fail to meet what FDA set out as too rigid standards. We don't want that or the other direction, right, Brandon? Your comments on that. And then I want to go to the Ming for his thinking about how FDA is doing research to that regard.

>> Brandon: Sure, I vie it as some what separate and distinct separations. What I mean by that is general framework is needed in order to make sure we're headed in the right direction. I think whether or not there's too much specificity of the requirements, I think generally at least forward facing, the agency is open and industry is very accepting of alternative approaches provided that the mean, the primary end point is satisfied. That we're getting what we want out of the studies so I think alternative approaches are welcomed with an industry. I just don't know we're seeing that come to fruition from an application review perspective. So if we're utilizing an alternative approach, oftentimes that is heavily scrutinized to the point you go back and conduct what was originally documented. Even if it might have been after the fact because then, you know there's going to be a smoother pathway with reaching approve ability with that kind of a design. A general framework helps to make sure we're getting in the right direction.

I am not necessarily concerned with too much specificity as long as the agency is open to alternative approaches and I'm not sure we have seen it on the industry side, at least from my perspective. I don't know if Meenakshi has any additional comments there.

>> Luke: But you wouldn't be privy where the alternative the are provided, exactly! You had a question, Meenakshi, do you want to respond to that?

>> Meenakshi: Are you able to hear me? I just wanted to say, sometimes during the review, we may get additional requests to provide the data. So even if we provide our alternative methods, there's always an expectation, you generate the data with the published methods so maybe in that case, it is like, really becoming difficult because we have to generate

everything once again and even the R & D is costly and it is time consuming so maybe from that perspective, if those expectations are clear, which methods we have to follow, maybe during the product development meetings, if the FDA has insights they want data for a specific method, that would be helpful. Not providing very specific inputs in the product specific guidances, however, our general expectations could be helpful for like, what type of methods are available. So I think that kind of information would be helpful. If not, providing very specific important things in the PSG. This is my perspective.

>> Luke: I'm going to Xiaoming.

>> Xiaoming: I appreciate the comments especially the presentation from the industry. I thought about in terms of the specificity and the details. You talked about the biggest hurdle is the detail. That's where a lot of research needs to flush out what we understand. Yes, in the beginning, the research is not just to get this published or the guidance being published. That's just to get started. So our learning continues throughout the whole life cycle of the product, from the development and industry perspective as you have the pre-ANDA submission, the questions, raised to the agency to consider the input from that point onward, and then, additionally, during the review, we keep learning and all of that, I think, is the opportunities for us to understand what is the detail we need to answer especially for the complex product, and complex generics, a lot of characterization and methodology.

What is expected, that's a question as in, we all should consider and certainly, industry and what I would encourage is to continue thinking, thinking outside of the box, continue to innovate and continue to propose the new innovative approaches and certainly from the FDA, we will also strive to improve our understanding as well. So a lot of our internal research is really aimed to address some of these gaps, filling in these details. And certainly we have done it through the publication sharing presentations with the public so that information and knowledge can be readily available.

The last point I want to mention also is that even though FDA we're doing research where we're publishing the methodologies as you heard in the talk as well, by no means, these procedural or the methodology used in the publication is what we expect to see from you in the submission because

recognizing that again, maybe it's too specific or prescriptive and the situation may change depending on the type of application and type of product and type of situation. So we do recognize that and also, that's something that I think, open dialogue between the industry and FDA needs to be considered either during the pre- ANDA and the ANDA assessment. That's something I think is very important to continue dialogue in that regard.

>> Luke: Xiaoming, that's nicely said! It epitomizes my viewpoint and that of many, that this whole generic drug development enterprise is a reflection of our learning organization values. Like, we are constantly learning from both the applications coming in with the research we're doing and then we're outputting and teaching others and moving ahead to come and get the best product going out to the American public. Priyanka, did you want to talk about flexibility especially in the topical space? The transdermal area?

>> Priyanka: Yes, absolutely. As it relates to the flexibility in the approaches, we have all of the previous panelist. We have always tried to incorporate the best information available at the time in our product specific guidances. And general guides as well. They are available. But at the same time, what we have seen as we get more applications in, as we have interacted with the industry, within the scope of the pre- ANDA program, we have learned a lot about this. It's a feedback loop. When we learn, we evolve and then incorporate it in our responses to your specific process, or we incorporate them/and or, we incorporate them in our guidance over time. For the topical dermatology products, I think one of the examples that come to mind, of course, are in vitro permeation testing. This is something that we started recommending in 2016. We have implemented it over the last five to six years and we have learned a lot. This is something we have discussed extensively over the last year and we hope to take on our learnings and implement them through ouraround review processes as well. One thing I would like to highlight here, while we have flexibilities in implementing recommendations, at the same time, it becomes challenging. I saw a question in the chat a little while ago. It's basically asking can we implement the recommendations that you have for a product that meets the no difference criteria for a product that does not meet the no difference criteria.

These are areas where we run into challenges because now, an applicant is coming in with a product that does not meet the

recommendations within the PSG and alternative approach to mitigate that risk is not proposed and we are kind of, stuck with that application and in those situations, we have interaction with the agency to find a path for which we are mutually productive. I would be very very beneficial. We are of course, open to alternatives but engage too.

>> Luke: Thank you, I was looking at the questions but maybe Utpal, you can address it as well. I must say, our interface between the review division and the normal transdermal team has been really healthy. We have had lots and lots of good discussions trying to move these products out into approval. So a question of stating this, is not formally required for the topical products. By topical products, it could be dermal, transdermal but it's required for certain topical products is my understanding. For example, for certain solutions. However, my impression is that it is still expected to present these results. Would you comment on that Utpal?

>> Utpal: I can talk on general terms. Depending on the regulatory requirements in terms of what comes in as an ANDA in terms of what needs to be Q1 and Q2 and what doesn't and then there's certain approaches that are open if you have a Q1/Q2 product. Depending on the type of dosage form that we're dealing with, and so on, that will sort of determine the extent of the E data that we need. You know, if you have a solution product that is Q1, Q2 the same, generally speaking the sort of the amount of data we would need would be pretty low.

I did want to sort of add one comment as well back to sort of echoing what was mentioned earlier about being innovative and certainly at the review stage, what would be helpful and I think you'll see this in one of Dr. Ren's slides. Any time that an alternative approach is being recommended, I think it would be very helpful for the applicant to, as much as they can fully explain the background of the alternative approach, the relative importance of the different studies in the package, and really what may be the limitations as well for each of these studies. What that helps us do, as some of the other panelist mentioned, that helps us fully understand the product. And kind of think about what is the best path forward. So I think the bottom line is that we're kind of all in this together and we all learn from each other so to the extent that, the applications that come in are, you know, supportive of their own approach in terms of explanation and data, that's very helpful to move things forward.

>> Luke: I see there's a question directed to me in the chat. About the immunogenicity guidance and impurities. I want to respond, it depends on the product. For example, if the impurity is our incorrect sequences about the nucleotides, those can be potentially magnified or become problems in their own right. So the context of what is impure does matter and the context of modeling and providing impurities, we're open to hearing ideas and I think, I don't think we would quash any proposals that would come in. But you need to do the research to support those kinds of things. We don't have -- or we do have someone from OPQ. Do you want to address a little bit about the context of research towards impurity profiles for products with immunogenicity?

>> Xiaoming: Yes, so -- with the review. But I think, as the general, in general, I think, what is important in setting this link to what is the purpose of the measurement. So I will state that there.

>> Markham: That's great. And there's a question coming in about the product characterization of ANDA versus RLDs having similar specifications. Having difficulty understanding what sameness means and this is the age old question, what is sameness. Bill, you and I had a discussion about this over drinks some time ago. What is sameness? Did you want to discuss what sameness is?

>> Bill: My recollection is we cannot identify what sameness, exactly what is the sameness. Sometimes it's easier to think about what is too different rather than the same. So I don't know there's an answer to this age old question as you say but it's certainly an interesting one to ponder.

>> Markham: Brandon, do you have any questions about it?

>> Brandon: I don't have the answers, I just have more questions. It would be great if there was a magical 80 to 125 or something along that. I think we're all aware, that's not the case. I think one thing that would necessarily not answer the question but help support us. If there's certain statistical analysis that the agency felt more appropriate for evaluation of the physical- chemical parameters. I think that could be useful. Statistics always tell many stories but for example, bio population equivalence approach to looking at individual results for the molecular weight for an iron colloid product would be useful, it would be helpful to know if it could assist in terms of giving ourselves a good gauge on

pass/fail and any remediation activities that we need to incur.

But I know that doesn't answer the question but, if the agency ever had some steer on how they could interpret data relatively would be useful.

>> Markham: I think that's the good point. What is the relativeness of the sameness? You could be very different but if it's irrelevant, that difference is inconsequential. However, if something is slightly different but it's such a critical part of the product, then the sameness matters more. Would you agree with that, Meenakshi?

>> Meenakshi: Yes. This is like my recommendation. If you can just look for a case study, how you have like, fifty applications so what actually you have, considered around making this, that it is the same product and what you're saying about the critical quality attributes. So it may not be applicable for attributes but for some it may be critical. So a direction in that area would also be helpful. Maybe just go back and check what has been approved and you can approve applications so that would give an idea on that.

>> Markham: There's a question about research grant from FDA. While the question is about studies in immunogenicity in humans which could be a large expensive study, maybe we can answer the question, how does FDA provide research grants for some of these questions? How can someone propose a research project like the in vitro aspects to human immunogenicity?

>> Wang: Yes, sure! Any clinical studies are difficult to conduct for FDA as well, so I think to really identify what is the goal? So for our research, to make the best use of our GDUFA, we have to have an end point in mind, when we develop the research product, although we don't know what we don't know but at the same time, we're not dealing with the black box. So for this, the first step for immunogenicity, it could be very product specific. So conducting costly research, then we're trying to maximize the utilization in the end covering as many product the as possible. So first, we really need to learn more either through our internal own research as well as feedback on this, in terms of what are the areas of products that we should focus on. They are truly high risk products to begin with. And then we can discuss how to develop the strategies. I think, with in vivo characterization to better understand how, what may be the possible differences although it's very, it could be very, you know, manufacturing specific

and those, than to see where we start.

I think, like I commented earlier, for the generics, it's all comparative. So it's different from the new drug standpoint. So here, we have one to begin with. So then the difference is what we see and in certain scenarios, right? If we really trust the analytical characterization and this is comfortable with the profile, then even the product is known to have an immunogenicity risk, how much additional study do we really need to do to make it? Or to feel confident to give the final approval? All of these things we have learned throughout the workshop and all of these are questions that we really need to sit down and think through before we do anything further. But at the same time, if anyone knows, you know, who may be the group with more experiences, we can collaborate. Then that's also very helpful for us to know.

>> Markham: I also want to say there's a comment about how we prioritize our research. So we do prioritize research based on what we hear from industry. What we see as problems getting a certain complex product to approval and we have discussions at various levels like Bill, all of us. We would discuss what things we need to prioritize. What things we have PSGs that have yet to have further development on and then prioritize a research based on that. Priyanka, did you want to comment on how we prioritize research?

>> Priyanka: Absolutely. Thank you, Markham. Our process starts with this meeting when we hear from all of you about what the research needs are. We collect the research needs and we try to match up with the current research projects. When are some of the questions that you raise, that are addressed by both research programs that are already in play and if not, can we put forth new research programs which are typically posted early or late in the year in terms of requests of applications which is often referred to as an RFA or the second approach we have for soliciting feedback where we may know of a question but may not have the specific ideas about how to address that question. In those situations, we reach out to all of you and ask you for your input or thinking about the potential strategies for resolving that question. And also, we have a broad scope of internal research where some of the questions that come to us which may be more product specific, or which may need to be conducted internally, we have a very efficient research program internally which we leverage to be able to resolve these questions. So we can't -- once we have the input from all of you and from all of our internal

stakeholders, we basically triage them and implement them through the pathway.

>> Markham: Any comments about the research priorities you have provided and some of the thought processes on how industry would think about how you have decided what things you prioritize?

>> Brandon: A lot of the discussion in other sessions have been focused on the next five years and I agree, generally, there's a lot of alignment in terms of the critical areas that will help facilitate industry and get approval in some of these complex products. I would also, you know, have a slide nod to the CRCG. We have had a lot of great interactions with them and a lot of really important research going into certain problem areas so as an extension of that kind of acknowledgment, the CRCG is useful as well looking at the next five years and everything we have discussed, and just taking it forward in these types of forums and with CRCG and I would commend the agency in terms of a lot of great work being done. It's just, you know, it's going to be continued collaboration to make sure we're getting full use of the work.

>> Markham: I'm going to put in a request to the question space. For the industry out there who are participating and listening in, I hope you like what you are hearing and that Brandon and Meenakshi reflected your priorities accurately but if you have other priorities you think are important, please put them in the chat room Q & A and they can be captured there for us. So please make use of our public dialogue space for those who are listening into this. Thank you!

>> Meenakshi: Maybe Markham, I would like to go back to session one, the starting of the session yesterday. He has given an enterprise level of the research needed. That's the comprehensive dialogue that already happened. Maybe there's a panel discuss at the end of. We are aligned and we appreciate the collaboration and the research priorities are always taken into account. I would like to thank everyone from FDA staff in doing the efforts in that direction. Thank you!

>> Markham: Thank you, Meenakshi. I see a question about how much we talk to our new drug colleagues? Bill, do we talk a lot to our new drug colleagues?

>> Bill: I would say we do! I think we want to understand what they're doing in the new drug space. Sometimes the

regulations are different from what they expect and we expect are different but we do get dialogue from the scientific perspective and we understand where they're coming from, what works under their regulatory framework and how that scientific understanding can translate to our interpretation of the data and what data we need for approval. I would say we dialogue with the new drug side.

>> Markham: In my 27 years with the FDA, we have talked a lot. Utpal, do you think that's accurate?

>> Utpal: I agree with what Bill said, Markham. There's a number of areas whether it's in the guidance development space, not only product specific guidance but also looking at some more general guidance that we published. I think we talked with our new drug colleagues very frequently. Some life cycle management issues and so on. We have a very strong interaction with that group.

>> Markham: Brandon, any additional thoughts and Meenakshi, you too, on this space of how we are implementing the science into our day to day reviews and things like that. We mentioned PSGs as one tool but the actual reviews, like the approving products or not, based on our understanding of the science.

>> Brandon: Prior to before submission and after submission, we have made great use of the pre- ANDA meetings and early on, we would run into an issue this is a review issue and we can't provide a specific response which is counter intuitive which is why we're coming to the pre- ANDA meeting to have a discussion on a specific topic but we have seen a great improvement on the last calendar year plus. Even if it's not a direct answer, getting some good dialogue to understand the agency's perspective will give us some thought as well. So great use of the pre- ANDA product development meetings, presubmission meetings, et cetera, will only continue to become more valuable and then post submission, I think, you know, we have also seen improvement on mid cycle review meetings and I think, you know, the transparency there is greatly appreciated, it's definitely moving in the right direction. I think, agent industry is looking for additional transparency and I would be no different but I would say, we're moving in the right direction on these complex products and ultimately everyone is in favor of reducing the cycle times and time required for approval. We're all on the same team just trying to get to the finish line.

>> Markham: Thanks for bringing it up. I think we have a

couple new tools with the GDUFA 3 commitment letter. In that, there's a discussion about the mid, changes to the mid cycle review to enhance it a bit. And also potentially to add some scientific discussion after a CR goes out potentially as well. So I know there's regulatory spaces but potentially that could fuel additional research either in the part of FDA or in the part of industry. To get us to yes, right? That's our hope. Meenakshi, you were going to say something, go ahead.

>> Meenakshi: No, I completely agree with Brandon! So it's like, we're also using best user product specific meetings, product development meetings and part of our question, we ask, we get a good insight from FDA and some specifics that are specifically like the ANDA review. We have already spoken about it so in general, maybe a little bit on the product and development meeting. If we can maybe work on the time line, like the four to five months that is required and we have to provide the data package along with the meeting. So maybe something in that direction could be improvised. Like, if we can have some close request and provide data which would be helpful and if we can have some project managers assigned to the projects and if we can just discuss the issues with our products and how to go about it, would be beneficial in the future. In general, I think we're getting full support from FDA in all of our discussions.

>> Markham: As we can see in these meetings, when we get a meeting response, it's a multi- disciplinary response to that. So it's a matter of putting all of our heads together. That does take time to get a good response out before the meeting. We're running out of time.

>> Wang: If I could just chime in here. First of all, thank, Brandon and Meenakshi for your kind words in recognizing the improvement in our responses in pre- ANDAs. The same here. I think we also see the improvement in generic applicants in terms of preparing the package of completeness as well as asking for a more appropriate question. So for certain things we understand, you would like to know some feedback in terms of setting specific appropriate specifications but from the review perspective, they often have to determine the final -- based on the whole package that is not present in the time of meeting. So I think, really, like, Priyanka mentioned in her talk. The kind of questions, Brandon that you proposed. For example, a new, maybe a new statistical method, right? Or maybe establishing the sameness for a certain particular

product as well. That is a good discussion point to know. There is very product specific, right?

I could take this as one example. In terms of molecular weight or weight distribution or this kind of distribution that inherits it, is dependent variabilities is always very challenging for sameness determination. So what we are trying to do, really, is to build this based on the scientific foundation with sufficient justification, right? So even for like, the -- depending on the dosage form, the API. You have the difference in ten to twenty. This may not produce a difference in terms of clinical outcome for certain products while for other products, you have less than 5 to make a difference. What we're really trying to do is look at the specific data in a package to support why we're considering this as an equivalent. We need to take this into consideration whether it's the same or different but at the same type, that's why we need to know how you characterize your product.

>> Markham: On that note, we're running out of time and one minute away from our scheduled end of meeting. First of all, I want to thank all of the speakers and our panelist for a wonderful session and informative session and thought provoking session. Thank you all for your part in participating this. I appreciate it. With that, we're on to the -- Marie, go ahead.

>> Maria: Thanks, Markham. That's for the session speaker panelist. We really appreciate your input. Again, if you have any questions, please be sure to add those into our Q & A box. And also, as Markham had mentioned, FDA does welcome industry input on the research priority for the next five years years. If you would like to provide a formal comment, please do so on the public docket by June 10th. The link is in the chat and will continued to be posted throughout the day. We will now be taking our lunch break and returning promptly at 1 p.m. for session 7, the drug device combination products. Thanks, and we'll see you back in twenty minutes.

>> Karen: Good afternoon! Welcome back from your break. Welcome to session 7, drug device combination products. This is our last session for the day. I hope that all of our workshop attendees are having a good day in enjoying the GDUFA research workshop. This will focus on processes, challenges and research opportunities related to drug device combination product development and review. Whether the device constituent has a simple or complex design or a simple or complex user

interface, users of combination products must be able to navigate design differences without additional training when this occurs. This aspect is neither simple nor fast. Today, our session objectives are to review how the office of generic drug compares device interfaces for proposed generic products and their reference list of drugs.

In addition, we'll review how the office of surveillance and epidemiology uses comparative use human factor studies to evaluate the impact of other than minor differences between the reference listed drug, and the generic product user interfaces on user error rates when generic suggestion constitute occurs. In addition, we hope to explore and discuss the following topics. Both during the presentations and then during our panel discussion. We would like to look at how additional research can enhance our understanding of user interface design differences and how those differences impact successful drug delivery following generic drug device, combination product substitution. We would like to look at how to improve and standardize approaches for identifying and categorizing user interface differences and whether the differences are minor or other. We want to look at how to inform development of a more predictable and consistent framework for user interface differences assessment. In addition, sometimes industry has found there's a lack of data. How does this lack of data impede the design conduct of comparative use human factor studies?

Can we identify alternative study designs that can provide data to support the generic product being proposed has the same risk profile despite user interface differences from the RLD. And what are other challenges that we can address to help enhance development and assessment of generic drug device combination products. I would like to introduce you to our experts who will be contributing to our session today. Our spikers include Dr. Betsy, a medical officer and physician with the drug- device combination products team in the office of research and standards, in the office of generic drugs and she will be focusing on the pre- ANDA evaluation of drug delivery device constituents. Captain Irene is the deputy director of the medication error prevention and risk management office surveillance and epidemiology. She'll talk about the recommendations about how to approach this. Dr. Melissa, is a biomedical engineer, an expert in human factors and she will be focusing on the root analysis and root cause analysis.

Dr. Mary Beth, another human factors expert that will be

joining us to talk about how building a taxonomy can help create a consistent way to determine design differences between reference and generic combination products. Haley will be joining us from the memorial Institute and that'll be talking about how to leverage device functional assessment in order to clearly classify and evaluate user interface differences and finally, Tracy will be joining us with the industry perspective on how insufficiencies and published literature can really be a barrier for defining this. I hope you find this informative, interesting and help to stimulate questions that can contribute to our panel discussion.

When we begin the panel discussion, three other individuals will join us. Chirag Dr. Yapping is the executive director of device development and inhalation development and Dr. Elizabeth is a pharmacologist with our drug device combination products team in the office of research and standards in the office of generic drugs and we are very excited she can join us today and represent Betsy who unfortunately had a family emergency today and was unable to participate in our panel. So with this, I will turn it to the next speaker and I hope you all enjoy the next session. Thank you!

>> Betsy: Good afternoon, and welcome. My talk is going to provide definitions for the common use drugs in this pre- ANDA space and lay the foundation for the talks to come. For a generic product to be substitutable for the reference listed product, there's three criteria that must be met. The generic must be pharmaceutical equivalent, meaning the same active ingredient, dosage form, strength, route of administration and meets the same standards as the reference listed product. It must be bio equivalent which means there's no significant difference in the rate or extent of absorption of the active ingredient at the site of action and finally, to be therapeutically equivalent, the approved drug must demonstrate pharmaceutical equivalence, bioequivalence and then, it can be expected to have the same clinical affect and safety profile when administered to patients under the conditions specified in the labeling of the reference listed product. Since we are here to talk about complex drug device products, what is a combination product?

21CFR 3.2 defines a product as my product composed of a drug and a device, a biologic product and a device, a drug and biologic or any combination of the three. The office of combination products has classified 9 categories of combination products. Of these types, 1, 2, 4, 7, relate to drug

containing combination products and are the most common types we see for genetics. The following slides will show examples of each of these types of classifications.

Type 1 combination products are in a convenience kit or co-packaged. These are the most widely familiar to the audience and include things like a prefilled blister pack with a vile and the syringe and needle to administer the product and other things like medicine droppers, dose counters, measuring spoons and even rules of measurements that allow the user to measure out the dose of the drug to be applied. Type 2 combination drugs are also familiar to the audience. This is the prefilled drug delivery system. In this category, the sole purpose of the device is to deliver the drug. You can see from the illustration, some of the commonly used types of drug delivery systems are transdermal patches, the various inhalers, nasal sprays, prefilled syringe and autoinjectors or autopens. Type four combination products not only include the device and the drug but the device that coated or inside of the drug. The device has an additional category.

On the left side, you can see the nasal implant. On this, it not only delivers the corticoid steroid but has the mechanical function of maintaining the open of the nasal passage after a surgery. In the middle, you see the estrogen ring which gives a sustained release of contraceptions over time and the other is the smart pill like Abilify. And finally, the type 7 combination products which are less frequent. These are separate products that require cross labeling. Typically the NDA is approved at the same time of the device either through the PMA process or the 510K process. Most common example of these are a light activated drug not co packaged with the drug and device but are labeled specifically for a device. On the left hand side, you see this which is used for the identification of bladder cancer with the system here. This is another example of Striker which is the spy agent green, an green agent that has to be used with the system for the detection of this gynecology surgery and finally on the right, you can see the acid product that is used with the blue UV light.

So in general principles when evaluating combination products. The performance characteristics taken into consideration, the performance of the device constituent and its interaction and impact on drug delivery. However, this is not the focus of the comparative analysis which I will discuss in the following slides. For that, the user interface is the

critical piece that we evaluate and this is the focus in evaluation in a comparative analysis. In January of 2017, the FDA issued the comparative analysis and related comparative use human factor studies for drug device combination products submitted in an ANDA. It's this guidance that provides the framework for how the evaluations of a generic product should be done. Please note this guidance currently under revision.

Some of the key points from the draft guidance include the fact that the generic device does not need to be identical to the RLD. The difference in the user interface should be adequately analyzed, scientific justified and not necessarily precludable under ANDA. Some design differences, should be minimized in the early phases of drug development. There are certainly labeling differences that allowed but on a case by case basis.

The expectation is that the end users can use the generic combination product when it's substituted for the RLD without the interventions of a healthcare provider and without additional training prior to use. In addition, we recommend there's a baseline assessment for any identified differences and this is done through the comparative analysis. This is to determine whether any information is data and this is typically in the form of a comparative use human factor study or safety or effectiveness. It's assumed if it's bio equivalent, it will be safe and effective. So now, let's look at key definitions from the guidance. When is the user interface? That includes all components of a product for which the user interacts. So the labeling of the packaging, the delivery device and its constituent parts and any associated controls and displays.

An external clinical attribute is a feature that directly affects how the user will perform the critical case necessary to use or administer the drug product and the critical task is those tasks if performed incorrectly or not performed at all, would or could cause harm to the patient or to the user where harm is defined to include compromised medical care. What is the comparative analysis?

The guidance defines three sections to the comparative analysis. The physical comparison which includes the visual auditory, tactile examination, including, size, shape, feedback compared to the same features in the proposed generic drug device combination product. It's recommended to start in this area because changes in this section may affect how the critical tasks are performed and how the labeling will need to

be addressed. The comparative task analysis compares step by step each task that is required for the user to perform in order to successfully administer the product. And the labeling comparison includes a side by side, line by line comparison of the full prescribing information, the instructions for use, and any descriptions of the delivery device constituent part and the RLD. When performing your comparative analysis, in the context of the overall risk profile, there are three possible outcomes that can be assigned. One is no different. The second is a minor difference. Where a difference in comparison to the RLD does not effect the critical design attribute.

An other than minor difference, however, is a difference in the proposed generic user interface that may impact a critical external pact that will involve the administration of the product. So when you have done your comparative analysis, there's two outcomes, either complete or incomplete. If the analysis is deeped incomplete, it may involve one or more of the individual sections recommended in the guidance some of the errors we see, omitted task and sessions that are not permissible under the regulation.

This table lists the common examples of what we have found in incomplete comparative analysis. The difference may be identified but not categorized recommended in the difference and minor differences other than minor differences may be identified but they're not justified. The comparative task analysis, we frequently see that the difference in the physical feature is not linked to how the user will perform a specific task that may be affected by that change in the physical characteristic.

Additional, we are seeing a lot of user risk analysis instead of the comparative task analysis and I will explain the difference in the next slide. For the labeling comparisons, we frequently see things such as the preparation, to use the drug or cleaning steps that are required. In the upper right hand corner in the slide, you'll see an example of a URRA. This should be familiar to most of the audience if you have been involved in device development. You identify the task. Any potentially use errors that could occur while trying to perform that task and then a characterization of the potential harm that can be caused if it's done incompletely. In addition, you look at the risk mitigation strategy that you can control to prevent it from happening. In contrast, the comparative analysis shown in the left lower coroner is exactly what it says. It's a comparison of these features with the RLD and the

generic. So how a task is performed in the RLD product should be the same as a comparative task when it's performed in the proposed generic. So what are the key takeaways from this talk? A complete comparative analysis includes the physical comparison, a comparative task analysis, and a labeling comparison focused on the instructions for use.

During the ANDA review, all of the labeling components are availabled but in pre- ANDA space, only the instructions are used. Pre- ANDA assessment can provide feedback as to whether a proposed device may be appropriate for an ANDA solution and if there's any other than, minor differences between the user interface that might warrant submission of additional data to the FDA to support the differences don't alter the overall risk profile when compared to the RDL.

Generic product labeling should be the same, although some differences are permissible as described under regulation 21CFR314.94. So our recommendation to the industry is to make sure you read and understand the draft guidance, the comparative analysis and relative comparative use, human factor studies for a drug combination product submitted in ANDA. Throughout this product development, consider your user interface and the critical task required to be performed in the RLD product. Evaluate each of the risks associated with the differences. Between these interfaces. You want to perform iterative comparative analysis to speak to minimize the differences from the RLD.

You need to consider whether the user interface in terms of whether they impact an external critical design attribute that involves product administration. If your device design is final, then you need to consider whether any additional data beyond just the comparative analysis would be needed to support or justify any remaining user interface differences. And this for example is whether or not you need to perform a comparative use human factor study. We recommend you talk early and often with the FDA through controlled responses or pre- ANDA complex products. Finally, I would like to acknowledge these following people for the help in developing this presentation. And with that, thank you for your attention.

>> Hi, good afternoon! I'm excited to be a part of this year's generic drug science and research initiative public workshop. For those who aren't familiar with me. My name is Irene and I'm the deputy director so today, I'm going to talk about the

comparative use, human factor study for ANDA products. Here is a quick disclaimer, for work prepared by U.S. government employees representing their agencies, there's no copyright and these products can be produced freely. Reference to any marketed products is for illustrative purposes can be does not constitute an endorsement by the U.S. government, department of health and human services or the food and drug administration.

The objectives of this session is to describe what the objective of the comparative use human factor study is. We'll review the step in designing this study, and we'll present an example of the hypothetical study and then we'll review tips for submitting a CUHF protocol. This particular guidance focusing on the analysis of the proposed user interface for the drug combination product when compared to the user interface with the reference listed drug or the RLD. The guidance provides process overview that starts with comparative analysis or threshold analysis as noted in the guidance. Now, after comparative analysis is done, as a sponsor, you need to determine if there's any differences identified. FP the answer to that question is yes, NEN you have to take the step of determining whether the differences were minor. Now, if the differences were not minor or these are other designed differences as noted in guidance, this is where we encourage you to have further discussion with the agency. We would also need to determine whether additional information and or data such as data from a comparative human factor study, may be warranted. Remember, ANDA relies on FDA's finding on safety and effectiveness for RLD. Requires demonstration of sameness of a number of characteristics plus additional information to permit reliance. Generic combination products classified as therapeuticically equivalent to the referenced drug can produce the same clinical effect and safety profile as the RLD under the conditions specified in labeling.

So what does this really mean? I well, it means you're not establishing new safety and efficacy for the proposed generic product. Generic product is essentially confirming sameness to the reference listed drug. Therefore, we need to discuss the comparative approach. For the CUHF study, the objective is to demonstrate that the differences would not preclude the approval of the proposed product in an ANDA. Generally, these are simulated studies and generally a non inferiority study design is appropriate. The goal is to show that the patient experience using the generic combination product is no worse than that with the reference listed drug with some allowance for random variation.

So what steps do you need to take as the sponsor? First off, you want to identify who your users will be. FDA's focus is whether substitution can occur with a full expectation that the generic product will produce the same clinical effect and safety profile. Therefore, you should include current end users of the RLD. You should consider if your analysis indicates the specific sub population should be the focus of a study. And you can consider whether a difference in design would impact critical design for patients diagnosed with certain indications only. And in any case, you'll want to have some discussion with agency to ensure appropriateness of the end users that are recruited.

Secondly, you'll want to identify your delta. You should consider if there's existing literature or data that provides a baseline knowledge for the user rates for the RLD for the clinical task of interest. You need to demonstrate that the error rate is no greater than the error rate plus delta, where delta is an acceptable deviation above the error rate for the listed drug. Delta should take into account there is some allowance for random variance with the error rate for the reference listed drug expected. Delta should take into account the risk that any difference inout be prepared to justify how you derive delta in your submission. And then you want to decide on paired design or parallel design on the NI study. A paired design will generally be applicable and more efficient with respect to resources. Subjects should be randomly assigned to the sequence of use such as AB or BA to control for order effects. In a paired study design, each subject is his or her own control. With this type of study, the sample size is often smaller than that required for a parallel design. First, you would enroll subjects and then randomly assign each subject to one treatment and then the subject would receive the treatment not previously assigned before you ultimately analyze the data. The analysis must consider correlation within the subjects because success rates in the two treatment groups are not independent.

A parallel study design on the other hand usually requires larger sample sizes than the paired study design. In this case, you enroll subjects and randomly assign them to one or the other treatment. Either the subject will get the reference listed drug or the generic product. And then ultimately you would analyze the data. Statistical tests with these designs are straightforward than the paired design. Afterwards, you want to calculate your study sample size considering assumed

error rates and delta. Please keep in mind that the flip side is success rates and this becomes more important as we talk later. Typically the acceptable type 1 error probability or alpha would be set at 5 percent. What you're watching for are type 1 errors where you reject your true null hypothesis or type 2 error where you have non rejection of a false null hypothesis.

Ultimately, you want to consult your statisticians. This is extremely important! You need to have the right expertise to undertake this on your behalf. So you can ultimately ensure that the study you design will in fact, allow you to draw the conclusions you're hoping to make. Next, you submit your study protocol to the FDA and get feedback before initiating a CUHF study. This can be done via a control correspondence or a pre-ANDA meeting. It's worth underscoring you should wait to get the feedback before you proceed with the study. Once you have agreed upon protocol with the FDA, you'll proceed with conducting the study and during the study, you're going to observe error rates and success rates for the critical task. When observing the study, you can assign a binary value, 0 or 1 for users for each critical task performed where one is assigned to the successful task complete and zero to task failures.

Then you'll perform your statistical hypothesis test, comparing the upper bound of the appropriate level of confidence interval for the difference in event rates to delta. So your known hypothesis would be that the error rate for the generic product minus the error rate for the reference listed drug will be greater or equal to delta. Your alternate hypothesis is the error rate for the generic product minus the error rate for the reference listed drug is less than delta. Rejecting the null hypothesis in favor of the alternative hypothesis supports the claim of non inferiority as defined by delta. Alternatively, if the study design is based on success rates, then you would perform your statistical hypothesis test based on the following. Your known hypothesis is that the success rate with the reference to drug minus the success rate with the generic product would be greater or equal to delta. Your alternative hypothesis is that the success with the reference list the drug, is less than delta. And in this case, rejecting it in favor of the alternative hypothesis, supports the claim of non sue purity.

So let's walk through a hypothetical. Your RLD is an emergency use product marketed as prefilled syringe with a cap

that snaps off. Generic proposes a prefilled syringe that has a cap that threads off. It's determined only one minor issue exists. For the for example, we assume that cap removal is a critical task so we would consider that intended users may encounter more difficulty with twisting off the cap and in the substitution scenario, they're likely to try to snap the cap off as that's what they're accustomed to doing with the referenced listed drug. As we dive deeper. What we focus on is the task of cap removal. We want to specifically understand whether the patients will encounter difficulties and be unsuccessful at removing that cap. Each subject will operate both devices in this case where you're using a paired design for a study. We would randomize on the order and other details are put in place such as masking the devices.

In terms of the test, your known hypothesis is to understand what percent of those failing the goal in this case, removing the cap occurs removing it, minus the percent unable to remove it. Because in this example, we set delta at 10 percent, then the null hypothesis would indicate that based on this subtraction, it would fall greater or equal to 10 percent, the alternative hypothesis is you would fall at less than 10 percent. So in this example, your sample size of approximately 50 would be determined based on the assumption that 90% of subjects are able to correctly remove the cap. Let's pretend there's information in the literature. You have a type 1 error probability of no more than 1 percent and your correlate is set at 0.9.

Here's an example of the analysis. If you look at this particular table, you can see the attempts that were both successful and unsuccessful with the RLD as well as with the test product or the generic product. This stands for success and U stands for unsuccessful. So when we look at the outcome of the study, we see that the difference in fact does fall at less than delta, with delta less than 10 percent. The upper bound of the 90 percent confidence interval is less than the 10 percent margin which rules out a difference of greater than 10 percent with 95 percent confidence.

So this is like doing one sided test at the 0.5 level. Let's take the same example and run it in an alternative way. We're focused on the task of cap removal but here we'll look at success associated with the removal of the cap. Again, both subjectings operate both devices. This is a paired study design with randomized order of the subject. Other details are put in place as appropriate and here, we have listed the null

hypothesis and the alternative hypothesis. Here, when we look at the percent when successful with the reference listed drug and subtract out those successful to using the test product, if it's greater or equal to 10 percent, that's null. If it's less, that's our alternative hypothesis. So again, let's look at the example analysis here. S stands for successful, U for unsuccessful. The users both use the reference listed drug as well as the generic product and based on the outcome you see, especially pay attention to this number that is bolded, we determined that the upper bound of the 90 percent confidence interval is less than the 10 percent margin based on the difference. This rules out a difference of this, therefore, rejecting the known hypothesis in favor of the the alternative, supports the claim of non inferior as explained by this. So let's ends in the tips.

Firstly, clearly identifying the user interface design differences. You want to include your threshold or comparative analysis as part of your submission. You want to make sure that you clearly articulated where those design differences exist. You want to ensure that you recruit appropriate expertise to inform your statistical analysis plan. In other words, make sure you have run your tests by a statistician. Within your submission, you explain how you did this. It's helpful to the reviewers when you provide samples of your product. It helps them point out the threshold analysis.

I would also refer you the additional information available with the draft guide called contents of complete submission for threshold analysis and human factors and submissions to drug and biologic applications. Last, please wait on agency advice before you proceed with your study. Thank you for your attention today.

>> Welcome, everyone to my talk on the URRA and root cause analysis, the secret ingredients for effective comparative use human factors. I want to thank you all of the organizes and a warm welcome and hello to everyone joining today. A little bit about me. My name is Melissa and I'm the founder of human ability designs. I'm a biomedical engineer who got started in human factors when I actually became a late caregiver for my brother Matt who is a paralyzed army veteran. He has a high level spinal cord injury and various disabilities so I have been in the trenches of providing critical care to a patient in the home and I have also helped hundreds of clients meet the

FDA's human factor requirements on the drug and device sides of the agency and I'm really proud to say that I have had 100 percent submission success designing and implementing human factor programs to get safe and effective products on the market.

These products that are ultimately there to help patients receive the care they need for the involvement in this research. So I come here with a passion for good design and definitely rigorous human factor science and bring practical experience with both quantitative methods where my educational routes started and qualitative methods that make up the risk based human factors engineering process in supported most FDA's submissions. I want to recognize my collaborators who have been foundational to the success of the work I'm presenting today. Dr. Conrad is the project PI who leads our efforts along with University of Detroit Mercy graduate students, Julie and Carly. And Dr. Mary Beth and Molly are both important contributors to this work. So our team is mostly consultants who sit between FDA and industry. We're working to help advance the draft guidance related to generic drug development and how to identify and analyze user interface design differences to compare an RLD and propose generic on the ANDA pathway.

Ultimately, we're always taking a systems engineering approach to the science of human factors. The graphic on the right shows how the research is anchored through thinking about who is using a product, typically the healthcare professionals and lay users for generic products. We think about where it's used, including clinical and non clinical environments for generics and how it's used. The tasks that brings some degree of potential use errors and risk into the design, use of the design. Which means usually that risk is at the core of our comparative use method and we're looking to help sponsors provide the necessary evidence that FDA needs to determine if a proposed generic user interface is safe and effective. In support of an ANDA submission. Or work has many different stakeholders so most importantly, we're thinking about the end users who need safe and effective generic products. We're thinking about the ANDA reviewers who need a consistent way to conduct the review and industry consultants who need a reliable method and academic researchers who often support these comparative use evaluations.

So as we take a look at FDA's draft B guidance, we say, there's a proposed generic in RLD. The threshold analysis

systematically flushes out how the key components of the user interface and tasks or user interactions compare side by side. And then the comparative use method build on the threshold analysis for comparing any of those, other than minor interface differences.

This method asks the overall question, is the proposed device as effective or not worse than the RLD. So this comparative use method has unique research questions. Primarily because of the ANDA regulation. Here, FDA is asking sponsors to prove number one, they have the same safety profile as the RLD and number two, that the proposed generic can be substituted for the RLD without intervention of a healthcare professional and without additional training prior to use. Interesting research questions. So there's also been great debate in the industry over the comparative use method with the industry commenting on the draft guidance with two key concerns I want to highlight.

First of all, it's comparing concerns with FDA focused on user rates and acceptable deviance between the two user interfaces. And secondly, industry stakeholders want this analysis between the human factor validation study. Our team's research is a three year project where we're developing use related risk analysis comparative use human factors method with three aims that we're concurring. Aim number one, we're completing the lit review and stakeholder interviews to develop a body of knowledge related to existing comparative use methods. Aim to relates to developing a visual taxonomy in order to help stakeholders systematically analyze the design attributes to help I've, minor and other than minor differences and Mary Beth can talk about that in a bit.

And then aim three is where we will pull aim 1 and 2 together to develop the improved method which is a hybrid approach between the current draft, comparative use guidance and the CDRH final human factors guidance that relies heavily on the qualitative method that we all know. And is built upon the user race risk analysis. So for aim one, we conducted a lit search and launched our survey and stakeholder interviews with 19 respondents so far. It's still open and we would love to hear from those who would like to participate. Our respondents are experienced with threshold analysis for various kinds of combination products. We're seeing that industry finds it's -- if it would replace the human factors validation study for the proposed generic. We're also seeing a request for bringing use related risk and potential harm into the

analysis. The following participant comments illustrate key opinions we're happy to report match the approach we're taking with our method.

First comment mentions focuses on use error rates with the approach the industry is used to. Another participant mentions the lack in context of only using, only focusing on user rates along with the vagueness of selecting a statistical power that may lead to statistical issues and we know that usability publications are slim pickings in our industry which is problematic for this method.

And then, finally, there's some frustration with the inability to achieve state of the art use ability with only focusing on the equivalence which really points at the regulation itself, not just the method and could be an interesting discussion with the agency. Also in aim one, we have conducted an extensive literature review with one part on the URRA. A little history for you. The URAA was first mentioned in the 2016 draft guidance on related clinical study considerations in combination product design and development. The URRA is a pretty standard practice at this point in FDA submissions and it really serves as the backbone of the human factors validation study and brings the context of use related risk into the task analysis. So the main secret I'm sharing today, if there's no URRA comparison in the comparative use method, then there's really no way the human factors analysis can be complete.

So in slide shows a template that my company developed for sponsors to generate a successful URAA for FDA review. This is a tool available for free on my website. If you want to reach out and obtain a copy. You can see from the column headings, you start with the hire call task analysis on the far left and then move to the right, you populate task by task or line by line. The potential use there or the things that could go wrong while using the device. These we have started to populate with our literature search. There are also formative studies, FDA adverse event reporting systems and other sources of this information. Very important information and then we talking about the potential harms along with the variety and the user interface risk controls related to the different tasks.

As an actual example, here's a URAA we put together for the EpiPen, you can see the detailed task that start with removing the autoinjector from the carrier tube and holding it in the

right orientation of the hand. Because this is an emergency use product and potentially life saving product, all of the tasks will have a high severity rating linked to the potential use errors and then the risk controls of the user interface is quite important to note as well. For example, the color code, the autoinjector ends, the on device labeling, even the IFU. So this one would be for the RLD and then for the proposed generic, we're working on a comparative URRA at the core of our improved comparative use methodology. For aim three of our product which we're not working on but aiming towards, we'll be using a case study approach with a proposed generic compared to an RLD. Where we will have differences between the different labeling and devices so we have different features to dig into. We'll be merging the findings with the case study approach to develop our improved method. Our users in this study will be both RLD novice and experience. The RLD will highlight when the user errors may be due to negative transfer or when they use the new design incorrectly because they're used to the prior design. We're also interested in RLD novice users because we know substitutions in the real world may happen in the reverse direction where we're using the new generic is followed by the RLD. So this could be interesting. While we aren't there yet, one key improvement we know coming in our approach is a qualitative analysis which is the second ingredient in our improved method, the route cause analysis.

Another standard practice in the industry and fundamental to understanding the context of users within a human factors evaluation. The route cause analysis will help parse out the meaningful use errors so to speak because in our human factors analysis, we often have non design related issues or users that are irrelevant to the design of the user interface and we wouldn't want to count those. For example, study artifacts or use issues on the RLD that could even be improved with the proposed generic. So the route cause analysis is really a gold mine for determining those problematic device or labeling design attributes when comparing the RLD and proposed generic in our method. And finally, the route cause analysis can show design improvements because we'll have meaning behind.

Participants are key to provide the what, how, and why of accounting and we think this is the window of opportunity to understand when we have improvements or equivalents that meets the as good as requirement for the ANDA pathway. So our key takeaways is that number one, the use related risk analysis and route cause analysis is keys to an improved comparative use human factors method. Number two, both of these human factors

tools are foundational. Number three, they will ultimately help improve the task analysis and counting of use errors. Finally, the URRA and route cause analysis will provide the necessary tools and linkage and prioritization of use related risk and the data being compared. Now, you know our secret ingredients so thanks everyone!

>> Hello, thank you for inviting me to participate in this workshop. I'm excited to be here sharing my opinion and research for the building of a taxonomy for the design differences in combination products. Before I begin, a little background on who I am and where I work. I'm Mary Beth, principle of HS design which is a company that focuses on user centered design. We work across the practice of medicine with over forty years of experience in the field. My background is design. I have a Ph.D. in design and have been involved in the application of human factors. I'm co chair of the AAMI and I believe it happens or doesn't happen as a result of the design. The research I'm presenting today is a result of FDA' funded efforts with the excellent team including Megan, Melissa and Molly. Each of us bring unique strengths to our research program and have a successful history of collaborating on many different efforts. Please note, this research does correlate and build on the previous presentation by Melissa. She covers aims 1 and 3 and I'll cover 2. To reiterate, to identify and analyze user interface design differences that the impact substitute ability of an RLD proposed generic drug device combination product for the clearance of FDA ANDA. As Melissa covered aims 1 and 3. This is a taxonomy to systematically analyze the design attributes and identify minor and other design differences.

They say this a picture is worth a thousand words and we're going to find out if it has application for comparative use human factors. Let's start with the guidance. The guidance requests a completion of the threshold analysis and as a result, a determination of design differences are possible. They list a few options in describing the design differences. One, no design differences. When no differences are identified between the reference and the generic. Differences in design, if they are identified of the product, and that of the RLD, if present, these can either be minor or other. Minor design differences mean the design difference does not affect any external critical design attribute. Other is when the

differences in the design of the user interface may impact external critical design attribute that involves the administration of the product.

The impact is FDA may request for additional information -- in you have made improvements, you may want to rethink the improvements because you have more information to provide, sorry about that. The goal in I would being a taxonomy of design is to really be able to more consistently identify design differences and to just help clean up that world between what is a design difference, does it matter? Is minor or other? Is there a design difference? Let's look at this example here. This is an example of a side by side comparison. It's only the first part in determines the design differences. So let's take a stab at it. To the untrained eye, this can look exactly the same. They're all gradations, along the same rectangle, however to the trained eye, these are all three different. They vary in size, color and shadow. And assessing the design differences between a proposed generic and an RLD, it's important to determine not only what design differences exist but also whether or not they matter. This should rely on the use related risk analysis. And lastly, they do not impact the use.

The goal is to enable accurate dosing in a safe effective manner. This often requires a reduction in complexity. So design matters. These facts are driving the need for this. The fact remains that it depends on the context and person. Context matters. It can be variable. It can impact their user expectations depending on the environment and access to care. Furthermore, the user group characteristics matter because it impacts their ability to understand design. This may ultimately influence design use. Determining design differences of the physical design can be evidence. However, it is the interpretation of the user interface including labeling, training, that matters. And the case of a proposed generic versus RLD, design interpretation will largely be driven from the previous use of the RLD, however, naive users may interpret it through exploring the product in its features with reliance on the personal expectations of functionality, previous experience with the like item, therefore, building a mental model on how it should be used and have further expectations when the context changes. This speaks to the importance of robust and detailed task analysis. Specifically talking about aim 2, our goal is to build a taxonomy with RLD. Using ones that matters and the human factors used. This is appropriate because it's widely used in biological research and

education and previously applied in the medical field.

Currently, there's three analysis techniques that exist. Label by label. Side by side, line by line, describing the information and the delivery device constituent parts. Secondary, the comparative task analysis. It's the generic to the RLD. What are the tasks? What are they expected to do? What are the perception, cognition and action? And then the visual and tactile, the size, shape, visual, tactile, sensory input that would be coming back to you. Each of these can present with minimum visual language. They may not be comprehensively describing the attributes of these user interface that could pose more or less risk. They say in design, the devil is in the details and it could be that the devil is in the details in using these techniques as a determinant of design differences because depending on the rigger, it can be demonstrated.

Where there's a none risk, it could be perceived to promoting an identical, rather than safer user interface. We may be making improvements, and it will become evident but we're not promoting it in our guidance. So what are the attributes? In conducting the literature research, we found there's little in it. There's little published literature about specifically user interface designed attributes. What is there has an emphasis on changes customer behavior and promoting brand. As a designer, I can attest the majority of my colleagues have an affinity to design but not about writing it. However, there's a few descriptors worth noting. These include, color, shape, size, and material. They do translate to 2D design. For example, the shape of the font determines if it's serif or sans serif.

All things necessary in order to use or administer the drug product. This is a broad definition and difficult to reduce the practice to the individual elements. This lack of definition further exacerbates the situation in the defining design differences of critical design elements. It isn't until there's an agreed upon language this can be resolved. Our goal in building this tax onny is to categorize these enabling the consistent determination of the design differences. We are just getting started in building this taxonomy and I would like to share a few examples and welcome your feedback as we journey through this complex situation.

This is where we started. By taking a look from the designer's perspective, we ask a following question. What

aspects of the inhaler could be variable? This enables us to identify physical aspects of a product design which may be important. It started with the discussion. It opened up the doors to say, is this important? Is it not? What is the relationship back to the task analysis and how could these inhalers, how might be the use be impacted by these different designs?

Next, we started to gather examples of inhalers in order to develop a library. We maintain the viewpoint of the embodiness. The results produce this natural organization that is based off from the fundamental. Elbow design, cylinder design, disk design, ellipse, rectangle design. Each are represented by several permutations within these categories. From there, we noticed upon further exploration in each device, the category SDAGS and visual taxonomy changes. So you cannot just take the approach of selecting the book by the color. In the first example, by design, ones that look similar are for different things. It can change on the question it seeks to answer.

While the above continues to focus on the physical aspects of the two devices, we're also assessing the labeling of each. Based on the experience, we know these can look minor but hugely impact performance. Today, we generate the following possible categories for these classification and have just begun to develop a robust data set. For now, our research continues. We have only started this process, especially how it relates to the use of comparative human factors considering the overall consideration and categorizing that is included to make the taxonomy a useful tool and additional consideration and the relationship to other human factors processes such as the use related risk analysis and route cause will be included. I thank you for your attention today and look forward to your questions, feedback and comments. Thanks again!

>> Hello, good afternoon. My name is Haley and I'm an industrial and human factors engineer with the memorial institute. I hold a Bachelors Degree of science and design from the University of Cincinnati and human factors from -- University. I have several years of experience in product design as well as human factors engineering roles, focusing on multiple different device types including combination drug devices, neurotechnology products, and mechanical or robotic surgery and wound closure. So today, I will be presenting some research that we're conducting in conjunction with the FDA around opportunities to leverage device functional assessment

for classified and evaluating user interface differences.

Some of the topics I will cover today will focus on the overview of the current research and guidance around the ANDA submission process and supporting activities for the drug devices. I can touch on some of the current challenges that have been identified and opportunities for further research. And then in the second half of the presentation, I will focus on the current research that we're working on in this space including planned methodology and the human factors activities we'll be conducting. So as we know, generic device development is really key to reducing the cost of medical care and to increasing access to critical medications. In order to sustain this type of development, the FDA currently allows for ANDA submissions in lieu of follow a more robust human factors testing path.

So the goal of this ANDA submission is to show that the proposed combination drug device is comparable to the reference listed drug without needing additional training or healthcare provider assistance. In order to prove this, the current guidance suggests the use of a threshold analysis in order to assess and compare the attributes of the proposed design. Also to identify any new use related risks that might stem from the proposed design. So whether these are considered an improvement or simply just a difference, both of these do have the potential to introduce new risks based on the user's previous mental model. So if the substantial differences are found throughout this process, one of the commonly proposed method the is to utilize a comparative analysis.

So in looking a the current process and draft guidance around the ANDA submissions for generic combination drug devices, we have identified some challenges that might require further development and research. The challenges that we have identified fall in two different categories. In the first level, we look at assessing design differences. So the first challenge we have come across is the guidance of conducting a threshold analysis. This is the recommended approach but the in- depth guidance is not necessarily provided to help guide this involvement. The second that we have come across is during the process of identifying design differences, in that threshold analysis, these differences must be categorized as either no difference, minor difference, or other. The categorizing this may create challenges. So while general characteristics of each of these categories are outlined, it may be difficult to place a difference depending on the specific product due to the lack of clarity around these

categories. The third challenge we have come across is the classification of other differences when there's a substantial difference that is found. The current guidance states that a difference falls into the other category if differences in the UI might impact critical design attribute which involves the administration of the product.

It is unclear however, what is specifically meant by administration of the product. And finally, labeling exceptions are also allowed due to the assumed differences that will be necessary in the task analysis for generic devices compared to the RLD but while these exceptions are noted to be allowed, it's unclear to what extent the labeling is allowed to be different. The second category of challenges that we have identified is around comparative use human factor studies. So if there's design differences that are categorized as other found in threshold analysis, additional human factors might be required to validate the differences here. One of the common methodings for validating this is the use of the comparative use human factor study. So while these studies are the most commonly used in the recommended path of the current draft guidance, the studies are time consuming and costly due to the high sample size requirements. So alternatives are allowed, although they're not clearly outlined currently as to what is acceptable or what has the potential to be used. So in looking at the current draft guidance and what is outlined, we have identified further opportunities for research. The first opportunity is for design difference categories and the labeling exception guidance to be further designed and clarified. The second opportunity that we have identified is to better define which steps of the task analysis require an analysis for those design differences.

The third opportunity is to find other alternatives. The fourth is for the incorporation of use risk methodologies which may mean developing and evaluating a UFMEA between all of the devices that we're comparing that can help to provide additional data. And finally, while it's not required in the scope of this research, we have identified the further opportunity to assess the internal mechanics of the device just to see how these might vary between the RLD and the proposed generic device and how it could affect the user interface differences that are found.

In order to conduct research on these challenges and opportunities, we're proposing a multi- step approach using existing human centered design methodologies. The process will

start with the literature search in order to understand the current literature and any gaps in the research in this space. Then we'll move to the selection of devices for comparison. We'll evaluate the devices that we have selected. Then move into the categorizing of design differences and the development of new methods for categories. We'll move into the development of new methods for assessing the other design differences and finally, we'll incorporate these methods into other areas that may benefit from these. So to begin the research process, we did conduct a literature research using terms as drug delivery, switching, use errors and human factor research.

There's a few goals. First identify the area in which research has been conducted in assessing differences between the devices. The second goal is to identify where the research is not yet conducted and where those gap the may exist. Our next step is to select products for comparison and to conduct an evaluation. So during this phase, we have selected several different devices in order to conduct a threshold analysis for further guidance development and also to conduct the initial review. We did select injection pen devices for the scope of this research and we identified this in conjunction with the FDA based on several different factors such as the applicability and anticipated prevalence in future markets as well as the limited published data currently available for these devices. We did selection several pens that are identified as generic proposed devices and then selected one device in particular for use as the RLD comparator.

We selected these devices based on their similarities and differences. So we identified two different types of injection pens to be used in this research. One is the manual injection pen and the second is the semi- automated injection pen. We chose two different types in order to create a more robust assessment and to identify challenges related to substitutability. So both of these pen haves a similar pen like form factor. The manual requires the user to conduct all of the steps for use from preparation, all the way to injection. This also includes the use of force to manually depress the injection drug to deliver the drug.

The semi- automated one, likely has the user do the steps but it varies in which the user depresses the injection button to automate the disk delivery. The next step in this process is to evaluate and compare the devices that we have selected. So several aspects are evaluated during the threshold analysis process for each of these devices. We'll start by looking at

labeling and look at the IFU, packaging and device labeling and compare for differences. We'll do break down and risk assessment for each device. We'll develop and compare each of these for the device to identify any differences. Then we'll move into a physical device assessment, looking at aspects such as force requirements, feedback and DWOIS materials and finally, although it's not required for the scope of this project, we have identify at the opportunity to do a mechanical break down as well.

We'll assess the inner mechanics to understand if and how the inner mechanical differences could play a role in the UI differences that are identified. We think exploring this aspect might have the possibility to enhance some of the future guidance as well. So once all of the devices have been evaluated and the differences have been identified, we'll categorize each of these differences to a no difference, minor or other category. We'll also continue to explore the available literature to identify the potential opportunities for classifying devices. Our objective with this step is to help clarify the guidance around classifying design differences and also to propose any new methods for doing so.

So typically design characteristics that are identified as being substantially different will need to be categorized as other after that threshold analysis. If a design characteristic does fall into this category, it typically has a comparative use human factor study will need to be used in order to validate those differences. And as I previously mentioned, comparative use human factor studies do have a tendency to be lengthy and costly just due to the sample size required for these types of studies. So our goal at this step is to identify any possible alternatives that might be more efficient than the use of those comparative use human factor studies and that also provide that same level of validation.

So for any differences we identify in our work during this process, will also work to identify what the alternative methods might look like and any potential risks presented between what we're assessing. The final stage of our process is to leverage our findings and recommendations we have found over the course of the research in order to expand the applicability to other areas that might be relevant. So we'll look at gaps we have identified throughout this process to determine where we have slotted in the new research and guidance. The goal is to provide the guidance that could be applicable to other entities that might also need a more efficient method of assessing these designed differences. So

just to wrap up here, we have identified several challenges and opportunities for research around ANDA submission for generic combination devices. For proposing a multi- disciplinary approach to conduct this research in the hope we can provide enhanced methods for categorizing these design differences. We are hoping to identify alternative methods for assessing the other design methods as oppose to the traditional method of the comparative use human factor study.

A few of the outcomes we're hoping to achieve include the streamline guidance for more efficient ANDA submissions, decreased time for generic combination drug devices to reach the market and finally, for greater public access to generic combination drug devices. And that concludes my presentation for today. I would like to thank you for your time and I look forward to further discussion here in a few moments.

>> Thank you, everyone, for inviting me to present on the 2022 generic drug science initiative public workshop. The goal of my presentation is to provide an example of the gap in the published literature related to the device constituent parts. So why is the published literature so important? Basically, it's used throughout the product development. We use it during feasibility. We use the literature to help provide an in-depth understanding of user groups and user environments and an example would be understanding of teams to be more compliant with the medication measurement if the combination product was discreet and could be carried easily in a backpack. We also use it for risk management activities to identify potential risks. We use publish data to show predicate devices or similar devices in what use errors they have and then how can we mitigate it through our product and we also use it to help support the design requirements with clinical and end user context.

Here we demonstrate the linkage design controls between the device design controls and the drug design controls. So after target drug has been identified by the business unit, then across functional team helps determine the feasibility of the project. Do we have an in house device we already utilize for similar combination products or do we need to explore platform devices? These are single platforms that can be used across various user groups and disease states. And an example could be a pen injector where the manufacturer of the pen develops the device but does not develop the drug. They may sell the device to multiple drug manufacturers so human factor

assessment goes on to say, how close it the new concept? So we compare the external critical design attributes and evaluate the differences. So this helps the engineering and manufacturing team determine suitable design options to consider. For example, taking into consideration the use, the end users and patient population, we could find one size doesn't fit all. Based on the human factors assessment, we can see whether this is even possible. If so, what would the manufacturing impact of the design changes be? Does it require new equipment? So after we have finalized on desired devices, on the desired device, we communicate to the business unit, cost, expected development time line and if there's any early risk to the project schedule. So if it's approved, we move to the device development using design controls. This all can take several months to a year before we get to the NPA in the kick off design control process.

For this presentation, the literature search is focused on pen injectors and autoinjectors because they're well established in the market. So what is the inclusion criteria? First, I wanted to use the journal articles related to the use ability of the device. For example, if the study showed that it was multiple studies evaluating the safety and efficacy of the drug and the usability of the device is not the focus of the publication, it was not included. The other inclusion criteria consists of less than ten years, English and U.S. based studied. So I recognized studies outside of the United States can add a significant value but for this example of literature search, it's difficult to establish if the product was marketed in the U.S.. So terms like pen injector because the list is so high and autoinjectors, you can see, we had more than 900 results for that. So we lowered it down to these listed here. So you can see how many results with the total results of 1,184. By the time we included the inclusion criteria, this was actually 44. I categorize these. The human factors engineering testing, market, post market human testing studies and engineering lab testing. And the real world use, the majority of the publications reported subjective data. This is the satisfaction levels, the ease of use, confidence levels regarding self- injections. These types of studies provoid a lot of value for the originator during the development of the new product where the data from the preclinical human factors work and the real world usability are combined to demonstrate the overall safety profile of the product. However, during the development of the generic combination product, these types of studies generally don't have enough objective data to use. For example, in a phase three multi- centered global randomized open label 12 week

study, in patients with active moderate to severe rheumatoid arthritis, assess the robustness and usability of the autoinjection pen. They were randomized both, and they recorded the evaluation in home diaries and required to complete two part questionnaire to evaluate this. If there was a negative response, it was said product technical complaint and the device and diary was sent to the manufacturer for evaluation.

After the twelve week assessment phase, when asked about the overall level of satisfaction, 98 percent of patients reported they are satisfied, or very satisfied with the pen. Most patients indicated that the pen was easy or very easy to use and 98 percent thought it was short, very short, and 91 percent thought they were very confident to extremely confident about using the same pen for their injection in the future.

As you can see, this is very difficult to translate this data into a generic pen where we will follow the RLD. So the human factors engineering test, these publications are synthesized data, objective data where they reviewed the task analysis, use errors, use difficulties and route cause analysis. In post market human factor studies, this is the same drug but a different device. They may be post hoc analysis for a new indication for use and they may provide objective and subjective data such as ease of use, patient preference. They are not always powered to demonstrate superiority. As an example, they conducted a human factors study with untrained adolescence, comparing a single dose epinephrine, with an approved autoinjector.

This type of study is very useful to evaluate the task analysis, identify any new use errors, that we need to understand for our products and our patient populations and can potentially leverage the use error rates to future comparative human factor studies. And finally, the human factors engineering lab testing. This is where the data provides laboratory testing that can be used to support design requirements. This can be measurements of applied forces. For example, if you had a plate on your lap and you needed demonstrate the insertion force of the needle and how long it can be maintained while they're holding the injection in place for twenty seconds. This is the type of data we use for helping with the clinical justification and then the usability justification for the design requirements.

Here's an example to support the development of the generic

combination products. And their gaps that no matter the types of devices. I would like to propose that the FDA works in collaboration with professional organizations that focus on patient safety and usability of combination products such as ISMP, the national patient safety foundation to conduct human factors of the literature and human factor studies and publish the results so that the data can be applied consistently across manufacturers and establish the appropriate sign requirements. Thank you everyone for your time and attention today.

>> Karen: That is what happens when you don't have good precision. Thank you to all of the speakers for your outstanding presentations that have led to very thought provoking questions in our Q & A. To the attendees, please keep them coming. We'll get started with the questions we have already. We'll keep an eye on those that continue to come in. We have all of our speakers joining us today with the panel exception with the exception of Betsy and another one of our team members, Elizabeth who is representing our team in her place. And then as I mentioned earlier Walker from pharmaceuticals and Yen is joining us for the panel. So let's not waste time. Let's get started. The first question is actually the first one to come in. I will adjust this one and then we'll move to complex ones.

The first question is whether a buckle or sublingual film is classified as a drug device combination product and the answer is no. The entire drug dosage form and including the acting pharmaceutical ingredient and the excipients form the film and when you put it in the buckle area or below the tongue, it completely dissolves and there's nothing left afterwards. So CDER does not consider it to be a drug device combination product. I wanted to use this question as an opportunity to understand that the office of research and standards communicating often and as needed with our CDER experts to work with offices to try to consistently determine whether the product is a drug device combination or not. These officers work closely with our office of the combination products which is located in the office of of the commissioner of FDA and office of combination products is in turn, working with the product jurisdiction officers across all of the different centers to try to ensure that these discussions are occurring in a transparent way and that the determinations are being made in a consistent manner.

I wanted to let you know the internal process is ongoing

every day. Our second question is, how do you recommend altering comparative analysis when the unlisted drug is no longer on the market? I wanted to give that question towards Elizabeth.

>> Elizabeth: Thank you Karen for that question. There are times when the RLD may be off the market. What we generally recommend is that the ultimate comparison has to be your reference product, your test product against that RLD. Again, if you can't get that RLD and it's no longer on the market, then we encourage you to come to us through a controlled correspondence to help you with the product specifically and in general, I can state we really want to see you try to find as much information on the RLD that is publicly available. So try to look for the labeling can and find the imagines that you can find and then bridge the gaps in your comparative analysis using the available information. Now, you can also provide additional information through doing some comparisons with the reference standards or other generics that are for that. That may also include additional information throughout your comparative analysis but if you do have specific questions for each RLD that isn't available, we did look at those on a case by case basis. So we highly encourage you to contact us.

>> Karen: Thank you, Liz. Let's bounce around to get more people engaged in the conversation. This was one of the questions that came in and asked, if a reference listed drug has a disposable pen device, assuming an injection pen device and if the generic company wants to use a reusable injection device and carry out comparative use human factor studies, and the comparative issue establishes that humans can use the generics reusable pen device without any additional training, will the FDA accept such devices as substitutable for the reference listed drug device design? Before we get into the FDA regulatory piece because a lot of these questions that we have received definitely have a little bit in the FDA tilt to them. I wanted to reach out to our human factors experts who spoke today. Just to get their perspective on this particular situation from a human factors perspective about what types of concerns if any, this type of switch between a disposable and reusable device from RLD to generic might raise in your mind.

>> Melissa: I think in this case, it's a pretty big difference in a disposable or reusable pen on the surface if we look at the design and use case there. So I would recommend that you take it through your task analysis to start so you look at probably additional tasks for your usable injection device.

I think, given human factors as a process. Starting with the task analysis and running through formative studies would be important because in some cases with some users, some use environments this could be other than minor difference and I think about that. Also, the question of using a device without any additional training, I would be interested again in informative testing, how are you determining that because that's a unique question from the human factors perspective and we know that training is difficult with any medical product but especially with combination products so it's kind of a standard we look at.

Training versus no training. But I think it's a pretty complex question with a pretty big difference in the design so you might have to attach a new needle and have a disposable product that will work with the device to introduce users. You might have to reload a cartridge or something of that sort. If you look at diversity of users, again, even lay users, adult users, that brings in some difference and I think it depends on the drug space. So that's where, I think, formative testing becomes very important which isn't really talked about in the generic guidance at all. I know it's something we brought up in preparing for this panel but that's my opinion.

>> Karen: Thank you, Melissa. That's very helpful. Does anyone else from the human factors world or industry have any thoughts based on your professional experience before we have the FDA folks weigh in?

>> Tracy: I can talk from the industry way on that. From my point of view, I agree with Melissa. Going through your risk analysis and your task analysis is what else changes so what is the indication of the use for the medication and then who are the end users who would be using this. So you would go through the task analysis and see what other tasks you have added by saving, you know, by reusing the device and if those end users could complete the task and the capability of them. We also look at the use environment. So if the pen is going to be reused, where is it going to be stored? How? What additional materials do you need to store now? So to Melissa's example of cartridges, do you need a new place to store? Is that going to be now stored refrigeratored or room temperature? These are all key information that if they're not provided any additional training or medical intervention, they can miss key opportunities to keep the drug and device safe for the end users so those are things that I would definitely consider

moving forward before you decided that the sameness of the device is actually acceptable.

>> Karen: Thank you so much. I would like to invite Liz and Irene to comment on this. Let me just again, restate the question, this is a pen with a disposable pen device and a reusable pen device and if the study doesn't show an increase in error rates, is that okay? And I would also ask, would your comments or thoughts on this be any different if it was the reverse? And the RLD was the reusable pen and the generic was the disposable?

>> Irene: Sure, I'm happy to start. So I think in either direction, since you put it in at the end, Karen, in either direction, a lot of what is referred to stands true, right? In the end of the day, it's important to understand what has changed because this is something that is coming in as a generic, you assume that you're looking at the same users, assuming it's the same indications being pursued across the board and there aren't exclusivities or other things at play. But I think it's important to understand what the difference is and figure out how you examine them in a comparative context.

I wouldn't go so far as to say, it's out of the question. That it's not achievable through proper study and design but it has already been pointed out, there's quite a bit of hurdles and considerations that need to be taken into account. Certainly understanding what tasks now differ. I know system of the tasks that were alluded to. Like, fundamentally, there's a knowledge change that occurs because they may not recognize it's reusable and as such, may discard it after that use assuming there's not other physical attributes that have clued them to that. I think there's certainly differences and they need to be examined but I think that's where the data would be come important. I'm speaking more from the user interface human factors perspective and there's other considerations as well. So Liz?

>> Liz: Sure, thanks, Irene! Yes, so as I said, I'm going to again, I agree with Irene. I'm going to defer to her about that human factor perspective which we agree, we need to see the data and see how the tasks are done. But you have to consider other aspects of your product development. So when you're changing out the devices, this can impact your quality as well as your bio equivalent standards. So you have to look at the product as a whole. What I highly encourage folks to do, if you're thinking about these devices, come to the pre-

ANDA pathway because we can guide you through whether it's suitable for an ANDA or does it fall under some other pathway like a 505B2 and that way you can probably get a better start which area you may want to focus your development on. So I won't say it's not necessarily out of the scope but we have to see where the challenges may lie and figure out the aspects of your product could be impacted against the RLD. I highly encourage more dialogue with the pathway to help guide you through what may be concerning and what may not be.

>> Karen: Thanks, Liz! While we're on the hot seat, we have a related question that will ask for clarification about whether protocols for comparative use human factors studies, should be submitted in the pre- ANDA space through controlled correspondence or a meeting. And the other comment is, it's this person's understanding that the study protocols are typically not submitted in the pre- ANDA meetings. Please speak to that.

>> Liz: Sure, thanks for that question. I want to emphasize, yes, there's been questions about that. We don't prereview clinical protocols but what we can do to the pre- ANDA meeting pathway is guide you on the specific questions you could have about your protocol. So if you give us specific questions or specific things you're looking for, advice on, we can kind of help guide you on these specific questions you have related to this protocol so we can help, you know, evaluate these certain aspects. Again, it depends if you want to submit it through a controlled correspondence or pre- ANDA meeting pathway. If this is submitted through the controlled correspondence, we expect it complex and then we have a longer time frame so 128 pathway. So your pre- ANDA meeting would have a longer one. So in terms of time line, similar. Depending on if there's specific questions about the protocol, you can have a discussion or other aspects of your product development that you really want to talk about so you can ask multiple questions about the product, you know, hitting different aspects and then you would also have a chance to discuss that with the FDA, I would highly encourage you to go through the product development pre- ANDA pathway.

So depending on your goals for that product, you can either tailor your specific questions and the advice you're looking for from us.

>> Karen: Thank, Liz! I'm deciding where to go next here. I think I'm going to go to a regulatory question that reaches out

to the device regulations so I'm going to look to some contributions, I know we have someone who can weigh in on this as well. The question is, if the device constituent of the combination product is contracted or manufactured for an applicant, it the applicant also required to comply fully and maintain applicable documentation? For example, DHF, DMR, DHR, FMEA and risk analysis for the device constituent? I know there are regulations for part four reporting in the post marketing space that related to requirements for device related post marketing requirements for combination products. But I am not an expert in this area and would like to open it up to others to contribute based on their knowledge of this and their experience and complying with reporting regulations and other regulations for their drug device combination products.

>> Markham: So this is a deviation from the main focus which is the research that we need to get to where we want to be for these device products but, in general, the devices that are manufactured, if their cleared under 510K, they need to follow those regulations in manufacturing, et cetera. So that goes back to the original way that the device came on the market. If the device constituent is part of a combination product, in addition, it will need to meet other aspects for the drug product as well.

So those additional concerns will come in. This is, we have other folks in manufacturing who can further clarify these aspects and if there's specific questions regarding this, they can send it in as a control correspondence for their product particular circumstance.

>> Karen: Thank you, Markham. I appreciate that. Does anyone have any contributions to this question before we move on to the next one?

>> Yapping: Hi, Karen! It depends on what type of devices we're talking about, right? Some of them may just be off the shelf devices. Maybe type 1 devices. And CMO may have everything. And maybe we just co package. It depends if it's integrated or co packaged and the type of devices and then it depends on what kind of design controls required for the combination product. The device, normally, they only have the DHF or design controls for the device only. To me, it really depends on the individual devices.

>> Markham: Let's stay focused on -- these regulatory issues will add an additional lay of the land. We don't want to get

involved in here.

>> Karen: I will say, a lot of these questions we received, focus on processes and how to go about achieving these device user interface evaluations in a way that is useful for product development. But maybe as we're answering these questions, maybe we can think about challenges and where we're seeking additional information. So I hope the panelist will feel free to expound on that as we go.

>> Liz: Do you mind, Karen, if I ask a question? I just want to get the industry perspective on maybe what research areas we should focus on. Especially with maybe getting additional data when we have other design differences. What are the main challenges you're facing in terms of forming the comparative use human factor studies and what areas do you think we need to work on in order to get, to try to get better data coming in or have more guidance for you guys in terms of getting these submissions through when we're dealing with other design differences? I will open it up to anybody from your perspective. I see a hand raised.

>> Chirag: I can start. Part is on the non inferiority margin and allowable margin with the sample size and study design. Part of the challenges we face is how to determine the allowable margin, especially for complex devices where there's not a lot of information in the literature to be able to pull from. Oftentimes, we're going to be using formative studies but in these cases, the rate of users can vary depending on the user group and again, that doesn't do a great job of informing what that margin should be and the agency expectation so it would be good to understand if the agency has some thoughts around what is the expectation based on the classification, the emergency use versus preventable or the allowable margin can be regulated accordingly.

>> Irene: I want to thank him for jumping in there. You hit the nail on the head. This is an area in which a lot of research is needed. From a guidance perspective, we certainly talking about the importance of delta and the fact that delta is the under pinning for your statistical test but you are right! We are aware there is not a lot in the literature beyond certain emergency products to draw. So I would say this is a gray area for collaboration. Certainly in terms of research because we are interested in gaining more and with

each submission and study, we look at something more. But there needs to be a certain threshold if you will, of the evidence we can collect to say definitively or in one direction or another, what is appropriate. I think what I would advise is, you know, number one, let's think about the research opportunities and then number two, I think for industry, I would advice, when you come in, just help us understand how did you derive this, right? What is your under pinning and what happens about your assumption and how they may change the greater, the differences you have. But when you start, you're sort of starting from a position where you're hoping things are the same. We had a lot of discussion in the course of two days about what does it mean to say something is the same. You're starting from a position such they could be allowable in the ANDA pathway.

So from that perspective, you're making certain assumption about either success rates, error rates with the RLD. So helping us understand whether the assumption were derived. I think we're looking for reasonable underlying assumption and derivations and that's where we're starting from as we continue to build the evidence in this space. Thank you!

>> Karen: Thank you, Irene. Mary Beth, you have something to add as well?

>> Mary Beth: I do. The first part about Irene's point about the delta and you want to get to the minor or no design differences because that's your path of least resistance, so from my perspective, if we can clearly define what minor means, at what point is the design, what is acceptable and what is not acceptable? Have some examples or a clear definition about what constitutes minor. Then you would know everything else is in the other category. That's my threshold. Then I know that. If my target or goal is to be no design differences or the minor and the minor is acceptable, then define what minor is. If we know, clearly, you know, no design differences, it could also be better defined as well because no design differences could mean, I'm absolutely identical. That's probably impossible to say I'm absolutely identical because I'll always have color, font, some change that could seem minor but it could -- well, what's the threshold in terms of defining what it is? I think that's a significant help to try to mitigate some of that.

>> Karen: Thanks, Mary Beth. Irene, do you have another comment?

>> Irene: I would like to respond. Thank you for that input. One thing I could just remind folks and I say this from the perspective of thinking about this, not only in terms of generics for which obviously my OGD colleagues also have input. But also from the standpoint of there's some over flow of the thinking as we think about biosimilars and other areas that the agency governs.

So from that perspective, I would say be really careful about backing into a derivation of whether something is minor or not, as oppose to looking a the step wise approach as outlined in the guidance. Yes, I think people are hoping that they have quote on quote, minor differences but really, the determination is not about what is the clinical impact. Like, that's important. That's context that we want but that's a question that comes later. The start of the process really is just about first understanding what does differ. And identifying whether that difference may impact a critical impact or not. Those are just yes/no questions. Whether there's a difference or not, it may or may not impact a critical test, yes or no. But then from there, that's where the additional information, not always data because there's an a miss understanding, that just because you have another difference, that it automatically means you have a study and I have said it before in other forums and I'm saying it loud and clear here, that's not true. It doesn't absolutely mean you need to go down that road.

But, that's where engaging with the agency to determine what data or information could be helpful is important. What might be needed is important. So again, I just want to bring everyone back to, it's a step wise approach that will move forward, not backward.

>> Karen: I'm going to turn us a little bit now that we have sort of picked it. What is minor versus what is other. We have had a couple of questions and we had some discussions amongst ourselves as the panelist when we were preparing for today and there's related questions that popped up today about the use of formative data. And what is the relationship between formative data and comparative data and validated data that may have, you know, been in the new drug application for the reference listed drug, and might be in the published space. Is there a time when formative data and the totality of evidence that is provided with that, can substitute for comparative use human factor study or some other comparative

type of assessment between the RLD and generic user interfaces? I wanted to open that to everybody so that we can get the full range of perspectives and experiences on that because it seems to be, a hot topic.

>> Melissa: I want to bridge off of what Irene is saying. When products are required to just be regulated as the same or reviewed as the same and not micro, but we're kind of hearing stifling innovation and advancement where we might have RLDs that are problematic and this makes me think of the human factor process doesn't end once a product is on the market, right? We have post market data coming in. That's something very important in the URRA and looking at those users and when is actually happening. There's some frustration that ties to the regular itself and I don't know if that's on the table. You know, I know it's a long process to get changed but there is frustration from a user interface design and improvement standpoint. And I think you can particularly see it in labeling. A lot of RLD have archaic labeling and the regulations say it has to be the same. And just how can we advance having other than minor differences and be better? What would the agency be looking for that might not be a comparative study because I'm thinking, we're trying to do a comparative study with tasks that don't with one product versus the other, that's an open ended question, how can we research that and what evidence would the agency want?

>> Liz: This is a research area to look at. How can we bridge this gap? What research where we have a reasonable expectation and look at it and see the space opening up. We have to remember, we are talking about generics versus brand name. We're limited to the regulations allow us to do but that doesn't mean we want to stifle innovation either. What are the questions that will come up for that particular product that, maybe from a user interface perspective, how can we bridge this gap? And I think, we're opening up to see what research maybe you guys think is appropriate and you know, have that dialogue and discussion with you to see if maybe there's a pathway forward we haven't thought of or, there is data or information out there that we can start gathering in looking at it to kind of bridge these gaps because again, we do have our restrictions but we do understand you guys want to innovate as well.

So we have a balance between these things so maybe that's something that you guys, that we can put back on you but maybe there's something in the research that you're aware of that

could help us, you know, figure out where that balance may lie.

>> Irene: Thank you Liz for your comments. I'm going to jump on the back of those. I think it's important to understand that there's different requirements and different things dictated by the statute for each regulatory pathway. So FDA is definitely in favor of innovation and Melissa, you and I work together a long time and certainly, I can appreciate you know, from the human factor side of things, absolutely! The goal is to optimize system and person interaction. That's fundamentally what the discipline is about and absolutely, I think we understand that. Where it gets tricky is what regulatory pathway are we discussing?

So I would also remind folks, number one, reemphasize Liz's message about research. Absolutely! Open yourself to research that can allow you to explore the innovation but remind folking, there's multiple pathways in the agency so if there's something you want to do preclude you from coming in with ANDA or as a 505 so kind of putting it out there so people can understand. It's not FDA stifling information but about ensure that we're following the law. Thank you!

>> Karen: Great! Yapping, I see your hand.

>> Yapping: Quickly! This is a very important topic, right? Looking a the FDA guidance, typically the industry submits the analysis and if there's no major difference, then the comparative human factor is not warranted. So to me, it is really, you know, two extremes. One is the threshold analysis, it's very theoretical and then jumping to extensive comparative human factors. So can we just use something like, the formative or summative to justify the intense user populations? Can use the generic device? Don't have to be, you know, from the theoretical threshold analysis to jump to the comparative HF.

>> Karen: I would like to tie this question to one that raised an interesting scenario. If an applicant has procured the same device as the RLD and the drug component is the bio equipment, are comparative use human factors used in risk analysis, comparative task analysis on all of the other components of comparative analysis still needed? And you know, if the applicant is pursuing the same indication, it meets all of the other sameness qualifications that are defined by our ANDA regulations, how is using the exact same platform inform the types of data that FDA wants to see for that application? And

that seems to fit in this question of, is there anything in between? So again, I would like to hear more from industry about how you have approached these situations, if you have ever developed a product using the same platform? And the types of devices, as well as experience from the colleagues before we weigh in with the FDA.

>> Melissa: I haven't run into the situation but I think I would recommend that you would do a threshold analysis because you have to provide the documentation. So you know, you have to show that you have gone through that process. Which can only be proven or, you know, given the evidence that the agency needs to review, by showing them what they have asked nor the threshold analysis and going through process. That would be my recommendation.

>> Karen: Thank you. Chirag. I see your hand un.

>> Chirag: This is a good question. This is something we have discussed as well. If you think this as a process, it's meant to be safe and efficacious from the device perspective but in the event of RLD or in the market, and you pursuing the same device, if the RLD is already established, with the efficacy, does the process of doing the URA and all of the different steps of design control necessarily add further value or safety in the product if your product is identical in every aspect? I think this is probably a question where from the agency perspective, the expectation is that we need to need to meet the buckets of regulation and we have to follow the process. We should did a threshold analysis because that's the expectation but I would like to hear from the FDA team on what their mindset is on products like that.

>> Liz: I'm going to speak up. I will just reiterate what Melissa was saying. So that the comparative analysis is done. So if the device is the same, the labeling could be slightly different. There's some differences. We need the minimal amount of data to prove it's the same, even if the device is the same. That's kind of the minimum we look for in terms of that. I kind of want to steer the conversation in a direction where when we're looking for data, we want to see something comparative. So if a study is not the way you want to go to have comparative data, is there a way to bridge comparative data in another way that we can get the same kind of outcome or answers? Because for us, no matter what it is, we need to see some kind of comparison between the RLD product and test

product to really understand what the use errors are. So when you guys are doing human factor studies in other realms and you're comparing devices, have you looked at other ways to do them and we would be interested to hear from you guys, is there a way to bridge that gap or that knowledge gap because for us, we definitely want to see that comparison being done in some way.

>> Mary Beth: I'm sorry, I'll be quick. I think that a lot of human factor professionals do comparative human factor studies early in the design process without calling it comparative human factors. So the term comparative human factors really stems from this guidance even though we have been doing it for years. What I mean by that is, if you're in a traditional design process or even in, well, you have no use errors, right? You're going to know what you have done. You're going to compare existing products and look to see if there's a negative transfer of something that has happened. You may compare two devices so design A and B and C. We do it routinely as a practice but our methodology doesn't necessarily change but our reporting does. That's buried in the informative reports not asked nor the validation. It's just a matter of illiciting the right data and right report format that could give you the same rich qualitative information based on that risk analysis of the different designs because you would have sensed, if you have despaired designs, you would have a task analysis that is done on each one of those designs and you would be comparing it. It's just what level of do we go into it? But we're always doing it in the early design process. I just wanted to bring it up.

>> Karen: Part of that early process is comparing the device platform options against the referenced drug in the situation of generic development.

>> Mary Beth: Yes, exactly!

>> Liz: I think what you pointed out, a particular thing you said is comparative qualitative, versus quantitative. There's another key factor where you can see we ask for the quantitative, versus qualitative and that can be an area that, I have heard some discussion back and forth. I would open the floor but I'll let Yapping go.

>> Yapping: What I have found in this comparative threshold analysis is we have been focusing on the physical attributes

comparisons. The IFU comparisons. The labeling comparisons. But we often forget about the functionality comparisons. For example, if you have this same device as the RLD, the injection is different but in the threshold comparative analysis, we're not talking about this. If it's inhaler, we're not talking about the force comparison but just on at the labeling, maybe we need to prove more on the quantitative comparisons.

>> Karen: Irene has her hand up. I don't know if she's going to speak to the quantitative comparisons but let's get to that. Thank you for your point. Yapping.

>> Irene: I want to speak to that holistically, thinking about what you guys have provided. Thank you both. Mary Beth, I think your point is taken from the stand point that formative work obvious in a lot of cases is which option gets you to the outcome desired which may be, something that addresses a specific risk when we have more than one way to go when trying to design out a particular hazard that can be identified. I think that's true! I think where we're very interested to hear more and certainly see more research on, is whether it's sufficient qualitatively to make a determination of conclusive determination, because as you know, of course, these are not studies that are powered to answer this question. That's where we, I think, have historically been stuck. Scientifically, how do we draw the conclusion from that but very interested to the extent that industry wants to look into this and conduct the research in this space and try to give us more information there. That's my first point to Mary Beth to your comments. And yes, Yapping, one thing I would emphasize is when you do get the guidance actually, and of course, we know footnotes are often over looked but when you get the guidance carefully, it hopefully is clear that the intent from FDA is not to just look at physical or overt attributes but to also make sure, for example, when we talk about task analysis, there's a specific question. We don't say, does A line up with B but also, without using the term PCA, we're talking about the PCA over lay, the cognition, the perception of the action that goes over it. So I would just emphasize, it's not just physically what is happening but understanding also, cognitively what needs to be processed, for example, and where errors can occur in perception and cognition as well.

Also, to your point, when we talk about the attributes, for example, the physical comparison in the guidance. We do speak to the fact that we're looking at physical encompasses a lot of things, auditory feedback, tactile feedback and I think that's

where you captured some of those elements of, is it a detectable difference in force, for example, that might change, like, if you have a user population that has, you know, hand strength problems and that could become a very important difference, right? If it's something they're unable to exert the necessary force on. So these are things that the agency is absolutely interested in understanding when these analysis come to us.

>> Melissa: With our research team bridging the qualitative and quantitative approach is our goal. I think, as it was talked about today, the lack of research in our industry with use ability studies being published. I don't see it going anywhere any time soon. Trying to go strictly a large sample, quantitative, statistically powered study is going to be an uphill battle for quite some time to really get that meaningful data. And so that is what we're really looking at is how can we use the rich quantitative data we know from the validation studies and the FDA guidance there, that has taken ten years to get momentum behind. We still see problems and high rates of failures of studies being submitted. Just methodology and what the agency wants to see so we're looking at how can we kind of bridge the FDA's wanting scientific data and wanting that powered more clinical styled study and industry wanting the qualitative, low sample size and what they have kind of finally, we have learned to do well, sometimes, still needed agency feedback and meeting in the middle somehow to provide that evidence but I think, that, in my opinion and what I presented, the qualitative data is one of the richest sets and there's times when we go to design analysis and we put something inside of the engineering team and the designers think are glorious and it flat out fails. There's so much unpredictable in the drug space. There's a high bar we have to make sure people are getting their medication. So I think that people centered design in making sure that we do have a rich informative set, I would encourage FDA to start asking for the formative data in these drug product submissions because if we're just waiting until the end for the statistical study, there's a lot hidden along the way and the formative, qualitative style data is really going to power the evidence that the agency gets to review and again, putting everything into context for the review.

>> Karen: I wanted to follow up on that. Irene, I did see your hand. So I wanted to just provide feedback again to companies who are going through these developmental challenges.

To please look for the product specific guidances. Our office is looking hard to add more consistently in terms of language and combination products in regards to considerations for the best development. In addition, please use the pre- ANDA development meeting mechanism to come in and ask these types of questions around types of data and study designs and things like that. One of the questions we received earlier did ask questions about why FDA is not publishing data about all of the studies we have received for comparative use thus far. Really, with the drug device combination drug products, the volume, we're starting to see climb and we are waiting to sort of reach a threshold where we can perhaps, start changing some of our pre application advise based on a certain amount of data that we have seen in consistency and outcomes with these studies. And we're trying to think about how can we share what we have learned without sharing private proprietary data. And so that's something we struggle with every day. One of the questions we have back to our human factors experts in industry, is what do you think the barriers are to publication visibility studies that haven't come through FDA yet or perhaps have. What is holding back sharing in some type of depersonalized way outcomes from studies so that all of the industry might be able to benefit from that?

>> Mary Beth: I'm happy to answer that question. We don't publish the usability studies. If it's formative, they're not published because it could be that the methodologies, there's a perceived secret sauce in the methodology. People are competing for business so if it's a consultant, may not want to publish because their protocols or methods are special. We see it in the industry and recent conferences too where they say we have a great method of doing IFU research but they don't share what that is. We also don't see publications because it does air out the bad laundry. So if I'm having a validation study and it didn't go quite as well as I wanted, I know what the problems are and I am going to be sharing that willy nilly. Sometimes you see they are published but redacted. Recently I submitted for an article, a big study followed by the Gates Foundation and got results back from the reviewers, that my methodologies because I was following all of the standards and only had 15 people, that I was statistically irrelevant so there's a misconception on what institutes a good feasibility study on behalf of the journal articles and some of that will be fixed with the recent journal coming out but there's a whole host of reasons why, from a business perspective, it's a risk to the business. That we're not sharing it freely. That are things we need to culturally over come because it does make us

better when we share the methods. You all know, I share my methods openly and freely. I'm an open book because I think it makes us better.

>> Karen: Thank you Mary Beth. We're winding down. I want to address a couple of questions we had early on and take a turn to some interesting questions. One of our attendees asked how can you conduct a comparative analysis when the reference listed drug is not considered a combination product. So for example, the reference listed drug comes in a vile. And the proposed generic is in a prefilled syringe. This is a scenario we see all of the time. I will keep it short and sweet and see if Liz has anything to add. Basically we recommend that you walk through the steps of the comparative analysis. Even if you cannot access that reference listed drug in the vile, there's not a whole lot of variability between what viles that hold a drug look like. You can walk through the physical comparison even if it's some what mocked up between a drug presented in a vile and a drug presented in a prefilled syringe as well as the user tasks involved in getting that drug from the container closure it comes in, to the point it's ready for injection. In addition, you can hopefully find the labeling for the reference listed drug. Generally a drug that comes in a vile will not have instructions for use. So you may be creating your instructions for use by scratch. But we recognize these differences exist and acknowledging them and providing as much information as you can in a thoughtful manner that shows you have thought about these differences, as well as thought about how going to a vile with a prefilled syringe and user population and use scenario is what we're looking for.

I will stop there and see if Liz has anything to add as a very experienced reviewer.

>> Liz: I think this is a more regulatory question and you know, we do expect you to do some sort of comparison with the RLD even if we don't consider it a combination product. There's a user interface with that product but it's not with the device that is supplied with the product so we understand there's still going to be some differences in there and just provide any justifications or scientific rationale in the analysis. Yes, we didn't know it has an instruction for use and you created one. That's okay in certain scenarios. It may be appropriate or not. So it's okay. You just provide your justification and rationale within your analysis so we have a better understanding of that. So we do still expect you to provide some sort of comparison in just, you know, if you do have questions about that, feel free to come to us.

>> Karen: Another question for consideration for the panel. When a reference listed drug is approved for multiple indications and multiple populations, so maybe adults and children. Maybe there's multiple user populations. Maybe it's used by healthcare providers and patients or caregivers. How should these differences in end users and use scenarios be taken into consideration when designing a comparative human factor study? And what other factors should be considered in these situations?

>> Melissa: I think there's a standard process again. In use cases, you would start with your task analysis, your user environment profiles. With the RLD compared to an innovative generic, then you know, you should have the same users and indications and the like so it really comes back to your task analysis and thinking about the risk profile is where the richness is. I think oftentimes, and Irene can certainly say one way or another. Oftentimes healthcare professionals have a different stake but I think, again, if you look at the regulations and looking at the sameness, and just applying that across your user groups, it's an analysis this needs to happen across all user groups. I wouldn't just exclude one. I would still go through the process of thinking through a task and what is changing on your user interface and how that might introduce potential risk and harm to those different types of users so it becomes kind of a multistep analysis.

>> Irene: Thanks, Melissa! I agree with what you have said. I think the only thing I would add though is depending, it's all in the details. As I think, Mary Beth mentioned in her presentation. Depending what the difference is and what tasks it may impact, I think that's where different indications and core user populations will differ to those different indications. There may be opportunities for efficiencies but understanding if there's data, whether it's other data out there that would exist, that could be used to supplement what you're trying to articulate to the agency in terms of whether or not, even if you have identified a difference and even if it's an other difference, that doesn't again, necessarily mean you have to deal with this CUHF. There could be other data information that could be used. So when we talk about different populations, there's different opportunities with efficiencies as oppose to what needs to be studied and what other data use to substitute. So that's all I can add there. Thanks! But just one more plug, which is, think about the

research aspect of this given the topics of today's meeting.

>> Karen: So in the last two minutes, I would like to have a little bit of a rapid fire round and revisit an interesting question that is brought up in the discussion panel for session six which is: When is sameness and when is differences relevant? When do they really matter? And I wondered if we could sort of visit the topic of the relevance of sameness and the context of drug device combination products, engineering substitutions. These are complex products and I thought that the relevance of sameness was really relevant to our discussion here as well as potential user research. So I would love to go around the panel table and get last words and thoughts about that. And any other remains research ideas.

>> Tracy: I can start, Karen. One of the ways that I look at it personally is, and it was brought up in the last panel is, when does it become impactful. When do we anticipate, one of the aspects I look at, when does it anticipate the risk profile of the device? Does it increase by occurrence rate of a potential use error that now could have occurred? Does it increase the severity rating? Does it introduce a new harm that wasn't there before? So a lot of times on the sameness and the impact, bringing it back to the risk analysis and the assessment of that is how I would look at it too.

>> Melissa: I would say the power is in the data and the user data and what users think. I think it really depends and again, we can theorize and go through our human factors analysis but it really comes down to having data with intended users that mimic the actual use environment and bring that context of use because every user group is different and unique and has rich voices that we should be gathering data around.

>> Karen: I think that's a great place to finish! Thank you so much for your excite -- oh, sorry, Yapping has the comment. You can close it out, yapping.

>> Yaping: Sorry, thirty seconds, you're talking about what is support human factors or comparative threshold analysis but this is sometimes quite theoretical. The same device, some may say it's a minor risk and other companies may see a huge risk. So error is still not very -- it depends on each company. Back to you, Karen.

>> Karen: Thanks, Yaping. And thank you all to our speakers and panelist for this diverse and insightful conversation.

Thank you to the attendees for your interesting and thought provoking questions. If you have any additional questions or ideas about needed research, please respond to the docket or even to the still open Q & A session. And with that, I will turn it back over to Maria. Thank you so much!

>> Maria: Thank you so much, Karen and thank you to all of our session 7 speakers and panelist. What a rich discussion! As Karen mentioned to all of our attendees, if you have any additional comments or input into research to support these innovations, please submit a comment via the docket that will be open until June 10th. We'll be taking the last break of the day and workshop and returning promptly at 3:45 p.m. eastern. The time here in the United States for our final session, a panel discussion led by our office director, Dr. Robert on the next five years of research and we hope to see you back in about fifteen minutes.

>> Hello, everyone! Welcome back to our final workshop on the GDUFA. It's my pleasure to bring back some distinguished guests and have some final discussion around research priorities, and really take a big picture look at what we think the important directions for the generic industry are going to be over the next five years. So begin, let me introduce the people on our panel today. So we have Kevin Blake who joined us, then one of our morning speakers, Bob, Karen, and Rose, Jason, and Anna from the center of complex generics and Janet from Teva and welcome all of you, panelist for our discussion today. So just to give our framework to the discussion here. We have about an hour for a panel discussion. I want to break it up in four broad topics and within the topics, we'll see where our discussion takes us. First, we'll talk about oral dosage forms and then we'll move to products and complex generics and then we'll talk a little bit about robustness of the generic drug supply chain and drug shortages that research activities may be to resolve it. Four big areas, to give a little bit of time to give you a map of the discussion that we'll have around here. And again, just a reminder of what we're looking for in this workshop is trying to really dig out what are the most important research goals for the next five years. Thinking about that, we're bringing this panel together here and we want to think about, sort of this really most impactful research will depend on the bigger trends in the generic industry as a whole and the direction and most impactful research is impacted on some of the overall directions we see the generic industry taking as the most important aspects of that, going into the future. So I really

welcome all of our panelist to share their perspective from their situations within the different roles in the generic industry to help us at FDA to understand the decisioning you're making about where to invest and when does your portfolio look like in the future? What research activity and new approaches might encourage you to shift your portfolios into some of these directions. So that's the insight we're looking for here. I hope this is a fruitful and thoughtful discussion around that. So I want to kick off looking these doses. Specifically, like, the typical thoughts on, what's the most important thing that we can do in that area of the generic industry with respect to science and research and some of the other things we have heard about with the workshop that I would really like you to comment on in this area are, one, we are talking about biowaivers and reducing the in vivo studies through the biowaiver framework is one aspect. We also saw a lot about modeling and bio relevant dissolution and the value it may have. Again, to say, maybe there's a bioequivalence studies we don't need.

In our session on harmonization, there may be harmonization opportunities here and the perspective on what might be the most important aspects to work for in the scientific perspective as well as the session on nitrosamines and how you see these aspects of the unexpected quality impurity issues affecting where the industry is moving in terms of developing solid oral dosage forms and how much effort you're going to spend nitrosamines rather than developing new products. So I want to open up the panel discussion and give your perspective in this broad area.

>> Jason: Rob, I can start off. I think it's very interesting for me, I was able to attend a lot of the workshops but the area that really struck me as something I'm very delighted to see, the kind of innovation and the kind of efforts that are being made towards the nitrosamines and impurities in the last few years. I think maybe two years ago, right when we were entering COVID, and we had this workshop, I led a co moderated workshop and I think at this time, we were talking about the detection of nitrosamines and others and to see in the two years sense, to see industry and FDA really trying to get towards the route causes and when is the presence of nitrate and how are nitrosamines being formed in the different processes. I think this is an excellent step forward and I think it shows a lot of the proactive nature of finding the route causes of nitrosamines on the radar and using these approaches and strategies and the high resolution techniques to detect the lower levels is something that I was very delighted

to see and the science presented yesterday was something that I think is going to be interesting to see how that develops going forward. That's one of the impressions I had and some of the notes I made from the discussion yesterday.

>> Kiran: I'm from APOTEX and seeing the shift you're seeing, how you have seen they have become more prevalent, it does pose a challenge. I think the agency research in that space of understanding the importance of these and really to understand if they are actually posing the risk or not. There's two aspects to it. One is the development of analytical science to get down to the detection level where you want to see them is one aspect. The second aspect is whether it's really posing the risk. I think the understanding about that is very beneficial but I think to your point, controlling these and agency, a lot of agencies put out the guidance and methodologies they have described in there but I think you'll take it one level higher. It's now also, if you have to make a change in the formulation you heard from this session, developing the alternative B approaches or looking for biowaivers that you're making some minor adjustments in your formulations. That makes sense to look at for, like, I kind of spoke about how the modeling can be used when we're going for post approval changes beyond level two. Somehow, is there a link between how you do it and what you may have to do, even on other situations where you want to do a change to your formulation?

Because the generic industry is becoming more and more mature and as they become more and more mature, they have to make product changes as part of their ongoing life product cycle management. So research in that area is beneficial to look at alternatives from doing a bio equivalent study. Another thing I want to bring about is that the agency has given as part of the COVID- 19 priorities, we described a number of steps that have been taken to address the interruptions and protocol deviations and how to manage unexpected events. I think if the agency can take that and make this a little bit more broader, where you have an unexpected B event and outliers that cannot be explained, today, the only other alternative is to conduct a whole new bio study.

But if the agency can take what they have done as it relates to COVID- 19 and the approaches they have taken, if the research can be done to extend that and find out innovative ways and other methods used like AI or PK modeling to predict

the situations, and provide another recourse that would also be beneficial so thank you again!

>> Robert, thanks, Kiran.

>> Janet: Thanks! I just wanted to reiterate what Kiran and Jason mentioned. Yes, we have gone some way with tackling the nitrosamines and we're finding ourself in a bind where, you know, we are having to consider whether or not to reformulate and you know, of course, that can put a lot of strain and stress on the generics because that means, it has various implications that of course, if like Kiran says, we can do some modeling, et cetera, to address some of these requirements that would be definitely beneficial. But one of the things that struck me with this whole discussion too is, you know, there was a session where it was regarding the use of R & Ds from a reference from other sources. That struck me as something that you know, well, of course only the industry has asked the same question before but it's really something that would be beneficial if we could look further into that opportunity because there's other agencies who are already accepting this so perhaps, this is one area we could really address.

>> Rob: Okay, Bob?

>> Bob: Thanks, Rob! And I don't want to necessarily go and reiterate everything, Karen and Jason brought up but I think, you know, it's a bit of a double edged sword, the better the methods get, the more you see, right? That's not a bad thing. That's something we're all facing, if a product has been out there for some time, and now we have a better method and we see things at a certain level, that goes back to the point that Karen brought up about risk. We have to have the discussions about what is the actual risk from the safety perspective. I think the other piece to that is, if you're looking to mitigate based on whatever the route cause is, if it's the formulation or the new material, that goes to the point we can talk about it a little later but supply chain too. If you're looking at mitigating based on changing the supplier which then has some regulatory burden to it, potentially if it's a critical excipient, is there something robustly available to be able to make the changes. If that's the way you're going to mitigate. I think the last point I wanted to make is that, you know, not just stopping with the nitrosamines, the general ones listed in the guidance and the product specific ones but also, you know, the additional impurities that may cause concern and risk and having those discussions amongst industry and within FDA so we

can make sure, it's not just, we have gone through the whole process. If we look at it linearly, we're doing all of these assessments for nitrosamines and then specific assessment like impurities and for these impurity X so let's, think about how we can best do that. Especially with the analytical technology we have now.

>> Rob: Looking for other comments? So like, to close out this topic a little bit, you have heard a little bit about, in workshop about biowaivers. So I'm curious in your perspective of the industry, how much difference does it make to you if you're entering a market or not if there is sort of a pathway to say, for example, BCS waiver for a product versus a PK in vivo bio equivalent study? How significant is this shift in sort of the access and decision to enter a market?

>> Kiran: I can chime in and others can then. It depends on the molecule. As you look at the number of molecules that are coming, the newer molecules coming, sometimes it's the risk. There are products where you have to dose probably 20 tablets dose to get decent sensitivity for measuring the drug of the plasma concentration. So when you have specific products where doing the bio studies are becoming more and more complex and it's a risk to the patient depending on the type of product it is. So in those instances, it makes it more extremely important to work on those products because otherwise, the cost of, in those cases, in many cases, when you do a patient study, it becomes -- you sometimes don't see the benefit of going down the path for those products. Not sure what to expect in the ends of the day, so it really depends on the type of the product where we're having a biowaiver approach would make it more beneficial or make it more tolerable to start working on those products.

>> Rob: So like the example where there's a risk population involved. So I look at this. One area where like, I might suspect if it's a large market product, the BE study is not the critical factor if you think there's a big market in the end but my question is for, maybe all of you are big companies and you don't worry about in but in terms of the markets where they are smaller but there's medical needs for these products. Is that a case where the biowaiver might say, oh, I can supply that need and you know, we're at the margin. So we're looking, partly from our perspective of where we ought to prioritize say, let's look for products where maybe there's less competition. It depends if there's a smaller market. Is that a significant factor than drugs, like, just smaller chunks of

the market we could have passed by.

>> Kiran: I would agree with the older molecules there. That is probably what you're saying makes sense. If it's an option, you might consider those.

>> Roisin: It's that piece, it is also a product, like, it deserves a similar pathway in the U.S. versus other regions. The time to development, maybe products with less competition, there's not as much regulatory understanding going back and forth with the agency to try to get the scientific understanding in your development pathway and then the time it takes to develop the product and that can be a big discussion point in the industry. How long is it going to take us to get this product through in multiple regions so I think it's not just this piece of self, but it's probably layered on a couple more topics we have heard in the last few days.

>> Rob: We have heard about harmonization as well. When there's a waiver approach to say, oh, all of the agencies agree that the waiver approach, you can pass a little bit by the challenging issues on the reference product there. It doesn't mean we don't want to work on the reference issues but we have heard the value of the global reference product in terms of a value proposition from the harmonization side for the smaller molecules. So I want to do a final check in the area of the solid oral product before we move on so any final comments in that area from our panel?

So I want to discuss our discussion to talk about parental products and injectables and non complex injectables as well. I would like to comment, we have talked about complex products and non complex products. Sometimes there may be a third category, right? There's the tablets and capsules and oral solutions and simple commodity products and then parental products, not really distributed through a retail chain but very different. Maybe more concerns about the sterile manufacturing and then the chunk of complex generics and I'm wondering if it's a frame to help us think at FDA about where the generic industry's interest in invest wants cost of value doing something different might be to maybe map out that space of, there's something different about that. You know, when we talk about complex generics, sometimes the simple injectables get left out but they have complexities and things where regulatory science could help move things forward. So like, the two things I want to touch on here is one thing related to -- I can drill more on this in the Q1Q2 related question as

well. What from a scientific point has to be the same for an injectable product to be substituted. I would like to have some open ended discussion here and then probe in more. Is there some thought on the simple injectables that you could be face in this area?

>> One of the challenges is around PH adjuster, right? There's a new guidance that came out. The question is, does it help to answer all of the questions, right? Because there could still be challenges in regards to getting rejected for Q1/Q2 due to the PH adjustment. Is there more clarity to be provided, could it be pointed out?

>> Rob: The PH guidance that just came out, look, you can request it but the scientific question, first with PH and in the future with other types of changes is, what is the scientific questions that you have to evaluate to say, is my PH adjuster appropriate for use in a generic product? What do you think? You know, in some sense, if you say everything has to be the same as the reference product, we may hide us from thinking about what are the considerations I have to do to say, look, I'm looking at a product that has a difference and what supports that difference and I know some of you are in situations where you have taken a B2 pathway because you're using a formulation that is not the same. And your perspective on what is the scientific things you have to think about in these cases and what might be -- what work might we want to do that in the future, might say, there's a broader space for generic competitions in injectables that may have more differences in formulation. You can see, if that's the future, and how valuable is that future? To the generic industry? That's something that those regulatory changes that would have to happen to that, but there's scientific work that needs to lay the foundation. So the question then, you know, my question really is, if there's a future where there is more opportunity for generic competition with more differences in formulations for the injectables, how valuable is that future and how much investment is working towards laying the foundation for that, in that direction? That's what I really like to hear from you all in the panel.

>> Kiran: Rob, I kind of want you to factor the fact that in the future, under GDUFA 3, with the assumption it goes through and gets finalized and ratified, the petition, the pathway you're providing where the certification is going to be approved in a given time frame, and reason why it was brought

in as many you can see in the commitment language, is because, you want to give the opportunity for those injectable products that are not there today, mainly because of drug shortage. You want to bring those, give the opportunity to develop. So I think, if you look at that paradigm of what will happen with those kinds petitions going on. They bring nuances on the type of strains and formats coming in. So the science is needed to dive with the newer innovation in that space as it relates to the simple injectable product. One area that warrants discussion is allowing overages for products that are out there.

There's older products out there, where the brand itself has a degree of a percentage of overage and no one knows why because they're approved way back then. Now, when generic companies come in, the expectation is to be at an overage closer to the brand. So what happens if you're not the same as the brand in terms of the overage? I think this is something that needs to be answered I would say. Right now, we're so bound by what the overage of the brand is. These are all of the products so these need to be important.

>> Rob: That touches on the usability and is there an actual overage there. Do people depend on them and how the products are used. The interface of the clinical and substitution questions can come up. I think you made a good point about suitability which is another venue in which these questions will be opened. Suitability process, it's efficient and fast. We hope we'll get there, right? There may be more opportunities to say, this is the type of formulation that is petitionable. But you know, the perspectives on the value created and some of the challenges we see in this area. We say, wait a second, I have to be more concerned with the safety of an excipient if I want to make more changes or when do I need to be concerned with viability or immunogenicity? These are things that could come up in the area if you try to do things that are growing the scope of the products that fit into a generic drug approach.

>> Roisin: If it's one of the first things we're talking about when developing a product, if we don't think we can cross the barrier, we step back and say, are we in the position to develop? And so while the research may be a good idea to do, it might be helpful for industry to make discussions and even the FDA to make the suggestions because you could probably find there's a bit of a stand off because decisions are made, it looks too tough so we will do it somewhere else.

>> Rob: That's what I want to explore here. Some of the scientific challenges are hidden. Oh, the rule is there. If it doesn't fit there, I'm not thinking about that. So you know, if you saw it and even in the PH adjuster, you can say, oh, I have to start to think about this. You know, if you want to try. And certainly we welcome comments from the audience member to the docket as well is something we can consider as. You think of this in different contexts. What are the aspects of products we don't have focused on so much in the past that can be more important in the future as we think about the portfolio of products interested in the future. Let's go to Anna and Bob for comments.

>> Anna: I just want to open up a bit away from the Q1/Q2 and discuss a few issues in the industry brought up in our interviews with regard to the very simple products and one of them is related to shortages in parental products in viles and stoppers. Very long delays in the purchases, and people are waiting for nine months for stoppers and standard viles so there's a simple scientific challenge whether there's a company that had been using a different vile for a different product and has a lot of data on this other vile configuration in order to avoid shortages and looking to substitute and I think, under these constraints, a lot of the scientific challenges are around what is an extractable study design? Is it even feasible? Clearly, this is an acute problem because of the COVID shortages but it doesn't mean that it will not appear in the future. And shortages and parental products do persist. So I think industry would like to have some more research in greater flexibility around changes of the viles, and stopper configuration.

>> Rob: I think that's our final thought about containers.

>> Anna: So I understand. That's one item that brought up a lot and then the second one, is very simple but does come up with respect to the simple products. When there is the use improved method for impurity testing and the company buys -- that is approved many times by the API from the same source but just because there's analytical changes, like better methods are better, and just characterizing the impurity profile, now they find more impurities in their products and the RLD, it's becoming almost insurmountable challenge for them on how to discuss it and how to get these products approved even around the most simple products and I would say the people on the front lines more than center directors could comment on those

issues better than me.

>> Rob: Thanks, Anna. Bob?

>> Bob: So I won't belabor the drug shortage point because I was going to make that but the value proposition to have more flexibility when you're meeting drug shortage needs is very beneficial, not only the industry but the patients who know about the different shortages for injectable products. I think the value there is for things that are maybe not super complex but some what complex. You know, where the formulation may be a little bit more complex or have more ingredients than say the simple injectables. I think having more flexible there. And I was wondering as folks were speaking, is there a data set that can be mined in terms of, although there's Q1 and Q2 for approved products, are there characteristics of some of the excipients or API used even though it's Q1 and Q2 that can help us build data or information that would allow for more flexibility on some of the changes if we can kind of hone in on what those critical aspects are. So I'm just, kind of, that just kind of popped in my head as I was talking so I don't have it fully flushed out in my mind but just a thought.

>> Rob: Any other comments on parentals or injectables? Then we'll move to complex generics.

>> So one of the topics, and I don't know if we'll cover it later is immunogenicity. I think we have heard many times throughout the conference, a lot of excellent talks around that. So specifically, we have talked about peptides. There's been a lot of good talks and research from the FDA and others, however, could there be more, right? Could there be an even better framework work flow kind of flowchart talking about from where we were talking about the prediction and in vitro, for adaptive. HLA binding or T cell activity. When is enough enough? Can we just stop at HLA binding? That is around the adaptive piece. Also, could there be more guidance given around the HLA classify diversity, the subject, the type of experimental details truly wanted so we don't have to go back and forth in terms of understanding once the derivation of the assay, number of cells and the concentration of the product, so on and so forth. I'm going to open it up to see what others will say but I believe this is a great opportunity to help advance peptide medicines moving forward, thank you!

>> Rob: I know we had a session talking about some of the

challenges and implementation, right? And I see this as sort of the prototype of that. We support with research activities, both some of the in silico methods and newer approach to do that. We have been successful in the regulatory side internally of saying, look, immunogenicity for some of these peptides is not going to block generics. Really, a big significant shift internally in the thinking and risk management around this. But I think, he hits the point of where we are in this area. There's methods that are there. But really shorting them into an efficient system and a process hasn't happened yet. There's a lot of things you could do in the research labs but what's the thing that helps me say, that's managing the risk of this product. Here's the sort of agreed upon way to do that? That's an area of, I think that falls in the scope of the research. It's sort of a spectrum of, you know, novel science to be something that is implemented in sort of the regulatory science and development area and at some point in the far end of the spectrum, you get to the USP level and an agreed on systems standard and everything. There's a spectrum before you get there of activity. And that's what I'm hearing in that area. Other comments on that in terms of, how we're thinking about where we're at?

>> Kiran: I think I completely agree. This is a major problem. I think there's several platforms available for doing these immunogenicity assessments. However, there's a lack of clarity on the platform that is acceptable. And it's almost like, again, for the generic peptides, we do understand it's an evolving area, the immunogenicity assessment but the current practice and the tools that are used, they're varying significant by based on the experience, the scientific perception of the lab involved. So I think there's an opportunity to standardize things so we exactly know what is needed to what he said. We're not going in and circling through the lab again and again and coming back with major deficiencies. It's not really helpful so I think, although I acknowledge the point that you made, Robert, in terms of what the guidance is. But I can tell you, with regards to even peptides, we end up doing immunogenicity testing. Although the guidance says that it's, even if the impurity levels are comparable, our experience is it doesn't matter. You have to do the immunogenicity testing and that's becoming challenging to exactly all of the points that he said.

>> Janet: I don't want to repeat what was just said but that's definitely a pain point for us as well. It just seems like, you know, no matter what you do, you still have to keep giving

more. There's no specificity around what FDA really requires so you feel like you provide what FDA wants to see but for some reason, we keep getting additional comments from the agency and it just seems like a never ending sign. So I think this is definitely one of the top areas for further involvement.

>> Rob: I think that's a -- if there's a big set of products affected by this, in places where you really want to bring generic competition in for the newer peptides, it's an important area. Having some really, workshops really focus on implementation and practice and what to do is what I'm hearing here. Which methods to implement and how to implement it in a way that gets it right the first time in trying to figure out what the reason is and why it's not happening.

>> Robert, one more closing remarks for this is innate immunogenicity, especially when the impurity profile is clean, is immunogenicity truly needed? I can see for specific impurity if it's above a certain limit, fine, I get it but around the innate immunogenicity, something for the FDA to think about, is it value added or should resource be added somewhere elsewhere it co be value added medicine for the patient. Thank you!

>> Kiran: I echo what he said, Rob. It's not just the application but the need for doing this for scientific peptides. Although the guidance gives you clarity around it but how it gets applied for a review is very different.

>> Rob: I think immunogenicity has a lot of, at least perceived risks around it. There's a lot of cautiousness there. A lot of the scientific work can help say where do you really need to do that and frankly frame that debate and provide data around that. So I want to move our discussion around complex generics. Some of the things you have heard, talks a little bit about the immunogenicity. We have been successful in generating scientific approaches but there's some implementation challenges in getting at this. So that's one thing we have heard there. Another aspect is the combination products so we are bringing thoughts around combination products and you know, we redefined things as combination products all of the time but if you look at newer products, many of the products that are newly approved have value for the patient and the innovation side of devices and things that might be devices or might be something else, like, software integrated aspects that affect that. That's one aspect of where we should focus on complex. What do we see in the area

of complex generics and what complexities are emerging. The other thing I have heard and want to get the perspective from this group on, probably the most areas where this still occurs in scientific and regulatory challenges for the inhalation products and long acting injectables are the places where in the near term, there's immediate work to move new study designs and new approaches forward, relative to other products. When I think about it in the topical area, we have clearly defined characterization and things like that. Topical and ophthalmics, the things visible but it's the inhalation and long acting injectables where the studies are more challenging and different approaches and new in vitro approaches. That's my sense of the complex products that are where the current challenges are. I will, sort of.

>> Jason: How much of a barrier for the industry, like high resolution mass speck approaches and the MDRS has been in discussion in several years now, and I think that we do have some publications in our lab. And FDA. We do publish and I know from the research support, the agency also funds a lot of external research but in industry, what kind of a barrier is it to have these high precision analytics for use to replace the original testing to have sensitive approaches and I know there's probably technological jump going on throughout this globally but also with that, in the lab myself, we know you can have the best instrument but you need the right expertise and the right data analytics as well.

So with all of these barriers that industry is seeing as well.

>> Anna: Maybe I can move quickly on this item. More around validation. It's a brand new method and an unrealistic expectation of using and applying this and releasing and validating this method. This is where a lot of concerns come from even for a simple method like, in vitro drug release from a complex suspension or liposomal products. There's a very strong expectation of methods being validated and yet, if you look at the specifics, even those are not reproducible by a lot. So since there's a real difficulty in validating some of these methods or particle size analysis and some expectation of the agency to be able to do image analysis and quantify this images. This COVID is especially difficult because there are, you know shortages and equipment failures around all of these complex imaging machines. And yet, there's a very strong expectation of multiple laws passing and those methods being quantifiable. So that's where the issues are. The fact that

some of these methods are untraditional. Sometimes, it's difficult to find the equipment. Some major generic companies have access to all of the equipment and then there's the issue more around the expectation around the validation and what data it can really produce.

>> To build on Anna's point, we have to split up in two pieces. One is routine tests and one is characterization testing. These are one off testing. You don't need an expert resource for a full FTE for an entire year. The question becomes is, what is the right laboratory you need to go to? Access to these CRs that have the technology can be challenging. Number two, hiring the right experts to interpret the data or to help you understand to get that data report and put it so access to talent becomes challenging and someone brought up high resolution mass spec. Here's a gray area. So you can think in one instance, yes. You can do it for characterization comparability but this method needs to be compatible once it's transferred to be QC organization, right? If something pops up, then they need to understand how to deal with that data. Do we always have a qualified expert on hand is another question so can that limit the use of such technologies moving technologies in the future?

>> Roisin: Rob, maybe one final point on the inhalation, this is research in the last couple of years, there's a little bit of a linkage to methods where you have products approved in the field and they're not bio equivalent to each other. And how can methods and validation of methods and research of that area support the other piece from the end point perspective? So there may be something in terms of language as well. That definitely can be, some more research in that area that would be needed specifically for that.

>> Rob: I think that's an area, you hear a lot about the different model based approaching during this meeting and I think that for these really unique situations like you have, high variability reference products, you really need a novel study design. I mean, the usual things you do are not going to work. So we certainly are looking for, we're engaging in research activities and what type of study designs are valuable for those cases and the model base where you integrate the results of the measures you do with the model to generalize the prediction can be very valuable for these more complicated inhalation systems and also some of the long acting injectables where you can say, look, how do I leverage the minimum amount of in vivo data I need about these long acting products? This

is still a little bit far for the implants. We can say, whether it's a purely in vitro approach is the right thing.

There are some big opportunities for producing more efficient use of the in vivo evaluations and integrating to a broader approach there. So this is an area in both of these cases where we see, you know, very unusual complex in vivo study designs that new approaches can really help make, be much more efficient.

>> Kiran: Since you spoke about complex products in general, I think one area where we think there's going to be some potential is trying to find in vitro methodology to serve as predictive models for sensetytive in vivo studies. This is one area where we see, there could be some work done. There's a lot of work done on the topical space and you can extrapolate the work you have done in the topical space to see if there's other methods we can look for additional mutation or sensitive. The other is the current AID guidance S that suitable for the topical administration? We're seeing that many of these competences there, like the inner membrane, I'm not sure if this is really relevant for transdermal products. So I think something to look at that, as you evolve in the future for transdermal products.

>> Rob: Kiran, specifically, what the challenge in the transdermal IAD?

>> Kiran: Yes, because I think nine out of times excipients we end up submits in a variety, we always have to submit a control, get the okay and it's always some kind of -- because the exact backing filament, inner markings that we tried to use are not always listed in the variety.

>> Rob: Because of the adhesives, okay.

>> Kiran: AID is probably not relevant when it comes to these transdermal products.

>> Roisin: I wanted to go back. You mentioned devices and I'll hit on that if it's okay. It will continue to be a huge explosion because it's becoming more complex and inherently a lot will require these delivery systems and maybe a couple of points to mention. And one is a very detailed discussion in the last session specifically around comparative use to human factor assessments and I think to make the point here again while we can, I think it's a huge area for people operating in

this space that we still have not a huge sense of clarity from the agency, maybe five years after the draft guidance was published? There really isn't a lot in the public domain in this space. This area is very complicated but I definitely think there's significant research that is needed in that area to move things forward because we haven't really moved the bar significantly in the last five years. We're starting to see it go a little bit but there's a huge amount to do and I would be a very big advocate for significant research in that area. And I think, secondly, a link to that and I don't think we talked about it over the last couple of days but I think it's an area that is becoming more complex and the devices we're developing are subject to certain patent reviews that we like in the drugs and that's often forgotten and we have a separate level of patent review making sure we can't, in our development of devices that are same and similar, other than that barrier of same and similar, they can't be exactly the same for patent reasons and often the regulatory framework and the legal framework don't marry off. The agency may say, you need to be the same color or a different color but legally, we may get a different opposing view and I think, some sort of research in this area around when it makes sense from the patient safety and risk perspective to be the same and if we can agree on that framework and maybe there's other areas where it's not so important. And I think some research will help and we can see it and it will be another barrier in the next couple of years so there's my couple of points.

>> Rob: Okay. Janet?

>> Janet: I just wanted to agree with what Roisin just mentioned. We definitely need more clarity and specificity regarding what the design for comparative use is. That would definitely be helpful as well as criteria on non inferiority margins and I also wanted to touch on some of what Kiran said regarding transdermal products. One of the areas that we find frustrating is with changes in, for example, adhesives. We know that automatically, FDA regards this as a major change even to TE may be a very simple change. It may just be a start in material that is being changed in an adhesive. It would be helpful to develop some kind of criteria around that regarding what. There might be instances where there's no direct impact on the finished dosage form. So you know, this is one area we can definitely look into.

Regarding inhalation products, I know in the public session, I brought up that the whole, issue of going to green

propellants. The modeling would be a very helpful. I know a lot of work has been done but we need answers from the agency as to how this change will be addressed. It certainly, you know, is not feasible for industry or generics to have to redo in vivo studies. This is one area we really need to focus on and that would ask the agency to focus on in order to assist with generics.

>> Rob: Let me follow up on the inhalation and the green. When we had the previous transition from propellants, it sort of ended up as basically, every product became a brand new product. There was never sort of an idea that within the scope of an approved generic application, I could move in that direction. Is that something that the industry feels is pressure or regulatory -- you know? Is this something that will, you know, that is driven by the generic industry as well saying, I'm moving to a greener propellant or is it something, like, you have to follow a reference product. Maybe that's the sense of how you may see it. I don't have an answer to this question but it's one aspect of trying to map out, where that is. Is it valuable to the generic industry to say, I have a product and I want to transition it in an environment friendly way, is this a vision or is it that, wait a second. You just have to wait until the brand of product the become environmentally and then match that? Is this the space of things that can be done on the generic side itself as part of the evolution and future direction of the industry. And you know, maybe you have the broader perspective on that as to how much you see that it's sort of an environmental sustainability being a factor in what the generic product of the future should look like.

>> Janet: It's a little bit of everything you have touched on. This is why we need this conversation. To see what is allowed. We obviously need to stay competitive and within the EPA's expectations so you know, if there's work that needs to change, we don't know what the expectation would be from the agency. Would generics also have to change? I mean, how would we compare on the market? Would we still be competitive? So there are a lot of unanswered questions and you know, at the end of the day, if the choice is that we want to move to or we have to move to a green propellant, what do we need to do?

>> Rob: Yes, there's a way to frame that in a future direction. So Rosario.

>> Rosario: I think there's opportunities for the FDA to

conduct research and make recommendations and set guiding principles for these connected device and smart devices. What is the FDA expecting to be extracted from the data? Is this part of a continuous clinical assessment? Some additional information in that area can set the direction as we're talking about the futuristic opportunities. Thank you!

>> Rob: Yes, this is definitely an area of uncertainty as to what that looks like. When I look to the future, I definitely see people are going to do things that create value another the inner face between software and pharmaceutical products. That's the reality of the future.

>> Roisin: Yes, I'm going to build on that. This is starting to become a discussion, with comparative use, what is allowable and not? How do we start this conversation? And I think even the discussion in that space would be welcomed because I think it's very unclear to the generic industry how it would be accepted and even pathways to have that discussion with the agency at this point from a comparative use, you know, device perspective if you think about the interface.

>> Rob: We have touched on this a little bit in some of the other areas but to talk a little bit about how I frame the supply chain robustness? Is there a scientific regulatory science work that can help in the generic industry moving to a situation where you have more flexibility in an environment where as we have seen through the pandemic, through various different interruptions, in maintaining the supplies and the essential medicines that U.S. and around the world depend on. Are there scientific challenges that if we address them, will make it easier to maintain it in normal operations and also emergency rooms. So just a broad way to get people thinking about it, areas related to excipient, to the active ingredient sources, to the device, the container closure and then finally, we just have reasonably well defined post approval changes for some are products -- like, let's get generics in and WHAES the post approval change work for enhilllation and how valuable is this? This is something you need to look at with the center of complex generics to kind of formulate some thoughts on this. This seems like something that is, you know, societally important. And well, national security importance as well. I welcome comments in this area to close out our discussion.

>> Roisin: Maybe more thinking in industry as much as the agency around how we can use comparable methods during predevelopment rather than waiting for the post approval

changes and in our space, just the time line can take a long time. So I think even if it's a conversation between industry and FDA in how we advance and kind of have these discussions earlier in development as part of those presubmission meetings would be very helpful.

>> Rob: On the scientific point, a lot of the change, the science for bioequivalence and efficient ways to show that, that's the same scientific question to bridge, I need to bridge from my pre and post change process so there's a way to leverage that understanding and you know, we just haven't put a lot of focus on being, you know, we said, look, the important thing is to be efficient in bioequivalence but there's an aspect of being, look, being able to bridge these other types of changes more efficiently might be something that creates value in this area.

And what are the sort of key biggest barriers here? This is something that we can welcome docket questions to say, if there's a specific area where, look, you can figure out how to do it better and then we would be able to move more quickly from A to B if need be.

>> Roisin: Certainly under the device of container, I would think there's principles that can be applied like, elastomers, resins, there's probably some general principles to applied if you want to make she's changes, these are the type of research and development data you need to generate it to support the change. So that's one of those three bullet points that are of value for sure.

>> Janet: I guess, I would just reiterate that as well. One of our main pain points is the lack of super guidance for a lot of these complex guidance. For example, if we wanted to make a side change for an enhalation type product, there's no super guidance that tells us that this is the things that -- these types of studies that you need to conduct. We may think, okay, in vitro studies are all we need but again, we're not -- it's not clear to us. And what we have found when we contact the FDA agency, we might get a blanket statement. This is a review issue or complex products so maybe you should just do an in vivo study. It's not very helpful and this is an opportunity to look closer to these issues if we want to ensure supply chain robustness.

The other issue which I touched on earlier again, is the reference issue. If we have the ability to maybe look at using reference products from other sources outside of the US, this

could potentially help with some of the supply chain issues we're observing because a global company like the one I work for, we may have different sites where we manufacture products but if it's a complex product and we need a bio study, you know, maybe an R & D from a different source could facilitate that type of study.

>> Kiran: I think not to kind of belabor the point but I think the key here is when you do these post approval changes, even for the guidance out there, or for the complex products, yes, understood for complex products you need a separate guidance but what are the opportunities? The main constraining factor where you don't want to do a change is because you have to do a bio study. So what can we do? What can with done using modeling, using mechanistic understanding, to get a waiver from doing the bio equivalent study? That would probably -- that's the crux of the issue you're seeing for these changes and as it relates to the supply chain. The other thing that I think you have spoken extensively over the last two days is the nitrosamines issue. That's an issue that absolutely has the ability, we have already seen it, on the impact it can cause to the supply chain. So I think, any research that can be done, one in terms of the AI for these complex nitrosamines using alternative approaches like, you have heard Martin talk about the molecular weight correction. So using alternative approaches when possible is going to be key when it comes to these nitrosamines and managing the supply chain continuity.

>> Thanks! Rosario?

>> Rosario: Just to build on what Janet said, the use of this for the development complex drugs could be phenomenal! It would help us advance and put together product development packages faster, especially if we get access to our RLD and the other point is to increase the regulatory burden is more efforts to use parallel scientific advice to align with the EU for complex generics. Thank you.

>> Rob: So we have reached almost the end of our time. If anyone has -- this is your final chance to raise your hand before I go to my closing remarks on my of the topics or any specific we haven't touched on here but I want to thank you all of you on the panel for your thoughtful comments on this and your perspectives on this. It's RR helpful to us to help understand where this sort of GDUFA science research program can help create long term value for our program and for our country and the patients that depend on generic drugs.

All right, with that, we'll move to our closing remarks. Perhaps there's a --

>> Recording stopped.

>> I'm going to stop the recording. Recording in progress.

>> Rob: So thank you, everyone! I'm the director of research and standards and office of generic drugs and it's my privilege to close out this two day workshop. It's been a fantastic workshop! It's our 10th workshop in this series since GDUFA one and we have gained fantastic insights into the value that science and research can create for the generic program and for the patients that depend on those generic products every day. And we look forward to increasing access, making a supply chain more robust, developing innovative versions of newly approved products quickly and efficiently through the support of this research program and we really appreciate all of the different people that have taken the time to provide their input into this. I want to thank some of the people, hopefully I don't miss any of them, who have helped make this event happen. So these are mainly people in, working a little bit behind the scenes. If you have been in the panel, you probably have interacted with them. I want to thank Sam, our associate director of science, for his leadership in this. I want to thank our project managers who you have seen, Maria and Savita who may have contacted with and heard from today, in keeping the logistics of working this, our great FDA staff that helped keep the internet stuff working and going and doing all of the registration for that. Our communications staff that helped us communicate this and make this available. We want to really appreciate the work that the center for complex generics has done in collaboration with FDA on this workshop. Making the immediate YouTube versions available. Helping Janet get input from across the generic industry and making this type of an event success and reaching out and find speakers for all of our different panels and collaborating them and we appreciate the support from the graphs and those at AAM as well in terms of discussing with us, at our biannual meetings and provided input in the agenda to make sure it's on focus and helping again, also, to recruit speakers that cover a wide range of perspectives from the generic industry and different size companies, different organizational roles within the companies who participate in this workshop.

I would like to thank all of the FDA staff who work as moderators for different sessions, or presenters or also, FDA's

staff working behind the scenes to taking notes from each session and make sure that we capture everything from this workshop. So what you'll be seeing from this is, you know, the YouTube events are live and you'll see it on FDA's website and recordings and is transcripts as well and then the follow up, you can see from this is we will go back internally and digest what we have learned from this event and then you'll be seeing in the fall, the sort of, for, hopefully for the approved GDUFA 3, the research priorities and the directions as we think about everything we have heard here and focus on the key aspects for our next five years of the research activities under GDUFA 3 should look like. So with that, I want to thank everyone for your attendance and participation and thank all of the people who have worked very hard on this and thank you all very much and have a great day!