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Session 3: Public Comments (Part 1 and Part 2)

Moderator:

Sam Raney, MS, PhD	Associate Director for Science & Chief Scientific Advisor, ORS, OGD, CDER, FDA

- **Public Comment Presentations and Open Public Comments**

- **Industry Interview Feedback on the Main Challenges in the Development of Complex Generics**
  Anna Schwendeman, PhD Co-Director, CRCG and Prof., Univ. of Michigan

- **Perspective of the U.S. Pharmacopeia on the Research Needed to Address Scientific Challenges for Generic Drugs**
  Prabhakar Reddy, PhD Director, Pharmaceutical Sciences, United States Pharmacopeia

Panel Discussion

In addition to moderators and presenters listed above:

Public Panelists:

Tausif Ahmed, MS, PhD	VP & Head, Biopharmaceutics & Bioequivalence, GCM, Dr. Reddy's Laboratories Ltd.
Pradeep Dabhi, PhD	Co-Founder and Chief Scientific Officer, Cutyx Research
William Ganley, PhD	Sr. Specialist, Nanopharm, an Aptar Pharma company
Andrew Graves, MS	Director, Immunogenicity Assessment, Specialty Bioanalytics, Teva
Ripen Misri, PhD Sr.	Director, Liquids & Specialty Dosage Forms, Global R&D, Apotex Inc.
Prabhakar Reddy, PhD	Director, Pharmaceutical Sciences, United States Pharmacopeia
Anna Schwendeman, PhD	Co-Director, CRCG and Prof., Univ. of Michigan
Thomas Tice, PhD Sr.	Director, Global Strategic and Technical Marketing, Health Care, Evonik Corp.

FDA Panelists:

Meng Hu, PhD	Team Lead, DQMM, ORS, OGD, CDER, FDA
Yan Wang, PhD	Acting Deputy Director, DTP I, ORS, OGD, CDER, FDA
Eric Pang, PhD	Senior Chemist, DTP I, ORS, OGD, CDER, FDA
Cameron Smith, PhD	Supervisory Chemist, DPQA-IV, OPQA-I, OPQ, CDER, FDA
Daniela Verthelyi, PhD	Supervisory Biologist, DPQR-IV, OPQR, OPQ, CDER, FDA
Deyi Zhang, PhD	Senior Chemist, DTP I, ORS, OGD, CDER, FDA
Lei Zhang, PhD	Deputy Director, ORS, OGD, CDER, FDA

Session 3: Public Comments - Part 1

Moderator: Good morning, everyone, and welcome to Day 2 of the FY 2024 Generic Drug Science and Research Initiatives Public Workshop. This is our GDUFA public workshop, and the purpose of the workshop is to identify what research the FDA should prioritize for FY 25. We already have several areas that have been identified as priority areas where research will establish the knowledge we need, build scientific bridges, and cover current knowledge gaps.

These knowledge gaps are currently creating specific problems or challenges either for generic product development, which our panel of industry and public representatives here can really help speak to, or problems for the FDA to assess and review data submitted about these products with our FDA panel that we have here as well.

My name is Sam Raney. I'm the Associate Director for Science and Chief Scientific Advisor in the Office of Research and Standards and the Office of Generic Drugs, and I help to oversee our GDUFA research portfolio. It's a large team of people that makes it happen from across the center, and we very much appreciate all the public comments that we'll be having.

Before we go into all of that, I'd like to introduce our panel. We have an illustrious panel of public and FDA panelists, including:

Public Panelists:
- Dr. Tausif Ahmed from Dr. Reddy's
- Dr. Pradeep Dabhi from Cutyx Research
- Dr. William Ganley from Nanopharm
- Dr. Andrew Graves from Teva
- Dr. Ripen Misri from Apotex
- Dr. Prabhakar Reddy from the United States Pharmacopeia
- Dr. Anna Schwendeman from the Center for Research on Complex Generics
- Dr. Thomas Tice from Evonik

FDA Panelists:
- Dr. Meng Hu
- Dr. Yan Wang
- Dr. Eric Pang
- Dr. Cameron Smith
- Dr. Daniela Verthelyi
- Dr. Deyi Zhang
- Dr. Lei Zhang

They are all experts in some of the different areas that the topics during this session will cover. We'll be covering them essentially as topic groups with public comment presenters who are here in person speaking first, and then virtual presenters speaking immediately after that. There will be five minutes per presentation. We'll be working very tightly on that schedule, and we'll have just a minute or two after each of the in-person public comments for us to have a dialogue.

What we're really trying to pull out during that time is identifying what is the specific research that is being proposed, how is this different than research that's already being done, and this is

where our FDA experts on the panel here are very familiar with the research in these areas and can hopefully comment on that. Then validating: would this research address something that is actually a challenge for industry or for the FDA?

With that, I want to thank you very much for being here and look forward to a very exciting and fast-paced session. I'd like to welcome up our first public comment speaker, Dr. Alexander Shankman from the University of Albany.

Public Comment Presentations

Alexander Shankman (University of Albany): Good morning. Thank you for inviting me to this exciting meeting. I want to very briefly introduce the challenge that is emerging.

This is about RNA-based drugs. RNA therapeutics is an emergent modality in drug therapy. It can target different agents in pathology. For example, RNA aptamers target proteins, siRNA (small interfering RNA) targets nucleic acids. It can also participate in protein replacement therapies, modalities such as mRNA.

There are 35 RNA drugs, some of them FDA-approved and some of them in clinical trials, and they're coming into the generic drug sphere soon enough.

The problem is that these RNA drugs have intrinsic susceptibility and problems, mostly related to the fact that RNA molecules are intrinsically unstable because of the presence of many bonds that can be hydrolyzed, like glycosidic bonds and phosphodiester bonds.

In the industry, there are a lot of chemical modifications of the bases and the sugars attempted to stabilize the structure. The second thing is that the delivery vehicles for these RNA drugs are usually lipid nanoparticles that introduce specific challenges.

With that, there is a need for analytical characterization of RNA therapeutics. Nowadays, the industry standard is liquid chromatography mass spectrometry techniques that do allow characterization of possible impurities and degradation products. But these are very cumbersome techniques and may not be within the reach of the generic drug industry.

What we are proposing is to use solution-based characterization techniques, such as nuclear magnetic resonance and vibrational spectroscopy approaches. These spectroscopy techniques can characterize emergent RNA therapeutics with minimal preparation. These techniques are very easy to interpret. They do not require sophisticated analytical chemists to interpret the results. They require minimal sample preparation, and importantly, they can be tunable to specific susceptible groups in the RNA therapeutics that can be quickly characterized.

They are able to characterize impurities fast and non-destructively. What is also very interesting about this particular characterization modality is that they can be used at the point of sale, which may be important for drug therapy that is intrinsically unstable.

Sam Raney: Thank you so much. That was excellent. It's a very good presentation about some challenges relating to analytical characterization of these oligonucleotides and some of the impurities. Do you have any questions for our industry colleagues or for our FDA colleagues about the specific challenges that they experience that this can address?

Alexander Shankman: Are there interests in developing at some point generic RNA drugs? Because this is an emergent area, and they're not within the realm of generics yet, but they are coming.

Yan Wang (FDA): Sorry, I have a question for you. When we do research, we're trying to maximize the value of our investment. Among the 35 products, what would be the potential model product you would choose? And what would be the potential for the method to be generalized?

Alexander Shankman: There are two very popular names now in RNA therapy. One of them is Macugen. This is directed towards macular degeneration. And Patisiran is directed towards neuropathy. That's probably the first thing that may come to the generic market because of the value in these products and being able to target diseases that previously could not be even targeted. But the challenges are in analytical characterization that is not very straightforward for RNA therapies.

Sam Raney: Thank you. Any questions or comments from our industry panel? We have 30 seconds.

Panelist: As you might have seen, there's greater interest in oligonucleotides in the industry to develop generics. Do you see application of this technology in oligonucleotides?

Alexander Shankman: Oh, absolutely. They are generally available to characterize DNA and RNA-type drugs because they probably will never use straight DNA. They will be modified. But both NMR and Raman spectroscopy or Fourier transform IR are very well tuned to characterize specific functional groups present in these drugs and can assess the integrity.

Sam Raney: I think we might actually continue this discussion during the panel discussion. That was wonderful. Thank you so much.

I'd like to welcome our next speaker, Marco Guerrini, from Italy. He's traveled probably on one the longest way to be here with us today.

Marco Guerrini (Istituto di Ricerche Chimiche e Biochimiche "G. Ronzoni, Milan, Italy): Good morning. I would like to thank Sam Raney and all the FDA panelists for inviting me and giving me the opportunity to present our data. I am the Director of the Istituto di Ricerche Chimiche e Biochimiche "G. Ronzoni" in Milan, Italy.

We started to collaborate with the FDA in 2008 during the heparin crisis when, together with the agency as an academic institution, we were able to discover the contaminant and disclose the structure of the contaminant in heparin. From that point, we developed analytical orthogonal techniques able to characterize heparin, but not only heparin—low molecular weight heparin, but also other complex drugs like polypeptides and oligonucleotides.

One of the drugs that is used in the market is defibrotide, which is a multi-target compound that is indicated for the treatment of hepatic veno-occlusive disease. It's a heterogeneous mixture of polydeoxyribonucleotides with high polydispersity, with a molecular weight average of 16 kilodaltons. It's composed of 90% single-stranded phosphodiester oligonucleotides and 10% double-stranded phosphodiester oligonucleotides.

The product is derived from the controlled depolymerization of porcine intestinal mucosa DNA, which in particular cases is a side product of heparin production.

From the guideline that the FDA provided last year, the fingerprint structure feature determination of this product is very challenging. We, together with other spectroscopy techniques like IR or Raman, think that NMR and LC-MS are the most useful techniques.

First of all, NMR—we can use different nuclei. I observe the same molecules by observing phosphorus. You can see that the reference does not still assign the free and the 5' terminal phosphate. The proton-carbon correlation also allowed us to determine quantitatively the ratio between different bases and ribose versus deoxyribose. And 13C NMR is also well informative, because the resolution, even though there is low sensitivity, needs high-sensitivity instruments to be interpreted and quantified. Also, proton NMR, particularly this region of proton NMR between 12 and 14 ppm, where the double-strand signals due to the double strand are present.

LC-MS is the other lead technique in this kind of characterization, and we can observe the intact oligonucleotides—obviously not all, but the low molecular weight part. You can see here the very complex heterogeneity, and we can reconstruct the LC profile looking for specific features like regular chains. We can see some other chains that contain two phosphate groups, 3' and 5' prime, but also structures that are modified, as was mentioned before in the previous talk, in which we have a loss of the base in the deoxyribose unit.

The most important thing is to characterize the process signatures, not the regular structure of DNA, and these signals can be due to possible oxidative damage during the process or the depolymerization, as we have seen before. These are the processing methods that must be identified and must be quantified in order to compare generic and brand drugs.

The other strategy is not only to look at the drug as it is, but also to depolymerize to reduce the sample complexity and fractionate. The fractions that we have seen before can be isolated and characterized using multiple different strategies, also LC-MS and NMR, but also 2D spectra with complex analysis and multivariate statistical analysis, like principal component analysis or other types of techniques.

I think all these orthogonal methods—only the coordination and the assembly of these orthogonal methods are able to identify and especially to compare a generic against the brand products.

Sam Raney: Thank you. Can you clarify in terms of the application of these orthogonal methods? What would be the research that you're proposing that we prioritize?

Marco Guerrini: The main research is to go deep into the structure, especially to identify these impurities. It's not easy and not absolutely easy to identify and quantify because, you know, LC-MS is a very good technique that has a problem for quantitative evaluation. So you have to use NMR. But in NMR, sometimes the sensitivity is not enough. So the isolation, the fractionation, and characterization of specific fractions could help a lot in this study.

It was demonstrated that some specific sequences bind thrombin, and thrombin inhibition is one of the activities of this drug. So in that case, it's very interesting to see if in some specific size, homogeneous fractions, these specific sequences are present, or at least to compare the

activity of these sequences. So there is a lot of work that has been done not only from a structural point of view, but also from a structure-activity relationship.

Sam Raney: Any questions from our panel?

Panelist: So you're asking us to investigate defibrotide or looking at more defibrotide. Is there any other product you think that we should also be looking into?

Marco Guerrini: The difficulties—defibrotide is one example. But we can study other types of drugs like high molecular weight DNA products that are in the market using the same approach. Obviously, if the molecular weight is increasing, you have to depolymerize and reduce the complexity.

Sam Raney: Fascinating, I think we had one additional question, but I wonder if we could, because we are out of time, hold that for the panel discussion, and we'll look forward to revisiting this during the panel discussion. Wonderful! Thank you so much.

Our next speaker is Professor Jace Jones coming to us from the University of Maryland

Jace Jones (University of Maryland): Thank you. It's a pleasure to be here. I appreciate the opportunity to share some of the research that we propose is needed.

The scientific problem is one that the previous speakers have touched upon: How do you support active ingredient assessments for generic drug development of phosphorothioate oligonucleotide therapeutics?

This really falls under a priority area. That's why I'm here. We, as biological chemists, think we can really develop novel analytical methods that will allow us to demonstrate sameness for oligonucleotide APIs (active pharmaceutical ingredients).

I don't think I have to go over this too much because the previous speakers have certainly introduced the idea of oligonucleotide therapeutics. I would mention that one of the nice things about oligonucleotide therapeutics is that they really fill a niche where small molecules and biologics have been successful, in large part because if you can identify messenger RNA or mRNA sequence, you can actually synthesize a therapeutic sequence that through Watson-Crick base pairing could be very specific and can actually hinder the messenger RNA breakdown or actually regulate gene expression. So it's proven to be a very popular platform for new drug development.

Another aspect of oligonucleotide drug development is that it's chemical synthesis. It happens through solid-phase chemical synthesis. Therefore, it provides you a lot of opportunity to impact or bias its pharmacological activity by introducing a number of modifications. These modifications can be seen in the sugar, in the base, even the backbone. So it provides, from a chemical standpoint, from a chemist's standpoint, the opportunity to have the most appropriate pharmacological activity in order to get your drug to a target and afford it to actually survive in our body.

One of the downsides of the chemical synthesis process is that you have a bunch of impurities, and once again, as the previous speakers have mentioned, these need to be characterized. The particular modification that we're interested in looking at is the phosphorothioate linkage. This happens where a non-bridging oxygen is replaced with a sulfur. So you transfer from a

phosphodiester to a phosphorothioate. This has some important implications in terms of pharmacological activity in terms of enhancing nuclease resistance, also in helping protein binding.

One of the downsides of this is you create a chiral center. So you have both your R and your S at that particular linkage. The number of diastereomers scales by 2 to the N. So if you have a 20-mer, you have 19 linkages. You have over 500,000 diastereomers in this particular drug complex.

We also know that the phosphorothioate stereochemistry affects the pharmacological properties and that the synthetic conditions affect the phosphorothioate stereochemistry. This has important implications for the active ingredient assessments.

If we look at, say, two particular drugs on the market right now—Biogen's ASO, which is Spinraza. It's a 20-mer, 19 linkages, over 500,000 stereoisomers. Now, how do you possibly characterize that many stereoisomers in a complex mixture? And then how do you then get a generic drug that has sameness? It's a challenge. Another challenge would be with siRNAs. This has considerably less phosphorothioate linkages. The terminal ends have the phosphorothioate linkages, but you have this duplex strand, and how that pairs can be affected by the phosphorus linkages. So it's also a challenge.

Considerations for sameness include the equivalent primary sequence, which is fairly straightforward. But it's really this diastereomeric composition. I realize I'm running out of time, so let me speed this up. In terms of guidance, at least for Spinraza, there is guidance to suggest that both R and S configuration ratios should be defined at each point in the oligonucleotide step, which is a challenge for generic drug development.

So what we're proposing is to develop a multi-dimensional analytical approach that really allows us to get to where we can have our reference listed drug and generic drug and be able to say how similar are they. We're using a number of different analytical techniques, be it LC, be it mass spectrometry, also ion mobility using gas-phase separation to fingerprint or profile, also using NMR.

There are certainly knowledge gaps that we think we can contribute to, in part by developing analytical methods that allow us to standardize this, but also being able to computationally develop models. So the research proposal—I apologize, I'm going fast here—is to computationally integrate high-resolution data for sensitive and robust determination of diastereomer composition. We think we can make this a quality control attribute. This is a collaborative project. We have computational biologists, synthetic chemists, and also an NMR specialist as well.

Sam Raney: Well, thank you very much.

[Audio interruption from ~26:22 to ~28:53]

Andrew Graves (Teva): We believe that the maturation behind the science or the science behind these assessments presents a timely opportunity to streamline and harmonize these approaches. Further research would aid both industry and the agency by establishing best practice approaches and perhaps broadening the utility of these assays.

The first point of research is that in the Holly paper that was published in 2021, they outlined the use of ten example formulations to establish the assay sensitivity of innate cytokine release assay for teriparatide. We previously posited at last year's workshop that a blinded validation experiment, using a mixture of formulations spiked and unspiked samples, could help to further establish the reliability and sensitivity of these platforms.

While the most sensitive assay is certainly desirable, each drug is formulated at different concentrations. For example, teriparatide at 250 micrograms per milliliter, liraglutide at 6 milligrams per milliliter, and that will likely impact the dilutions needed for the assay, and subsequently the assay sensitivity. So the research opportunity here is to establish the lowest acceptable sensitivity limits for any immunogenicity assays supporting ANDA submissions to provide further reliability that when sponsors are submitting, they're going to meet the requirements that the FDA would need in order to approve that product.

Our second opportunity is that in vitro immunogenicity assays have the potential to generate many data points which must be analyzed statistically to justify an outcome. A standardized or preferred statistical approach would aid in the analysis and understanding of these results. However, while the in vitro assays have been a good surrogate for clinical immunogenicity, there is no established link at this point between those results. I have a couple of examples. One is that if it's statistically significant, is that actually biologically meaningful?

Another example is if we wanted to test for equivalence, how should we set that equivalence margin? And the third example is how best to factor statistical testing in multi-factor assays such as the cytokine release, where you're measuring maybe 3 to 10 different cytokines. So the research opportunity here is to establish a standardized or preferred statistical approach for analysis of in vitro comparative immunogenicity results.

And our last opportunity that I wanted to mention was for recombinant generic peptides. The ANDA guidance I referenced from May of 2021 specifically provided guidance for the development of synthetic generic peptides, while analytical assays may provide descriptive results in the presence of contaminants, such as host cell proteins in recombinant peptide candidates. A fair, lingering question regarding the safety and immunogenicity of a recombinant generic compared to the RLD must be addressed.

With the advancement of the innate immunogenicity assay platforms like reporter cell lines and multi-factor human PBMC cytokine release, DC activation and so on, would these innate in vitro assays appropriately and sufficiently characterize the safety and immunogenicity concerns of a recombinant peptide candidate? And so the research opportunity here is to examine the utility of these innate immunogenicity assays for supporting recombinant peptide ANDA submissions. And with that, thank you for the opportunity.

Sam Raney: Thank you, Andrew. So actually, I'll begin with a question for our FDA colleagues. Since a lot of this relates to assessment and the evidence to support the assessment of ANDAs, can you comment on the research that's been proposed here?

Eric Pang (FDA): I'm just going to make a comment. Actually, these are very good questions, Andrew, and I think you're aware that we have the CRCG workshop. These are very good questions. We should be addressing these at the workshop.

FDA Panelist: I'm going to echo Eric's comments. These are excellent questions. Definitely among the next steps that we need to take. And I would add one more is that we need reference standards that are shared by everybody so that we can get to where you're trying to get. So thank you.

Sam Raney: Wonderful. So we might revisit this during the panel discussion. That'd be great. Thank you, Andrew.

I'd like to welcome our next speaker David Brahney, coming to us from Ginkgo Bioworks.

David Brahney (Ginkgo Bioworks): Thank you for the opportunity to present here today. Continuing in the same vein as Andrew's talk, I'm going to present on an idea that we have to carry out high-throughput immunogenicity testing of generic peptide and oligonucleotide and other complex biologic drugs using a high-throughput reconfigurable automation platform, a rack-based workflow. This is an idea that I've developed together with Professor Mark Davis of Stanford University School of Medicine.

So the problem statement: when we have these complex biologics, and here using semaglutide as an example, the process is indeed the product. And as Novo has revealed in some regulatory filings, the process to make semaglutide is at least a six-step hybrid chemical biological process, and there are several intermediates and some known impurities.

So when a generics company comes along and wants to develop their process, it's necessarily going to be somewhat different. They're going to have a different set of impurities and intermediates. And the question is, how can we reliably and rapidly assess whether their product is the same as the reference product in terms of its immunogenicity?

So the solution that we've proposed is to do this testing on human spleen organoids that Mark's lab has characterized extensively and to automate the process using racks. And this automation is continuing in the vein of what Ginkgo Bioworks does, where we're working with pharmaceutical partners across all modalities, from discovery to manufacturing using highly automated laboratories.

The gist of the idea is that one gets these human spleen organoids. They come from diverse MHC diverse donors. They are readily converted into organoids in Mark's lab. Testing is currently done in 96-well format. And we believe that the rack solution can automate this process and dramatically increase its throughput.

The organoids are actually immunized, as you would immunize a person by any substance that you want. And then the immune responses are characterized extensively. So cytokine panels speak to Mark's question about the statistical readouts, and cell proliferation complete B cell and T cell responses can be characterized.

Just a few data slides. Here is an example of a naive response to the yellow fever vaccine that shows that you get IgM and T cell responses. And then a second example with influenza virus, both inactivated or live attenuated. And here a novel multivalent nanoparticle that's carrying two different antigens, and you get a stimulated response by an immunodominant that actually provides T cell help to an immunorecessive immunogen.

One point here is that this system, we think, can provide the kind of data that one needs to train AI/ML models. This point was brought up yesterday about how do we get the data to even train and validate the models? We propose that this is such a way.

And then a natural extension of this idea is that the organoids can be used to test any substance, so certainly vaccines and adjuvants, but any drug that one expects, or maybe does not expect to have, any kind of immunomodulatory effect can be tested. So here is just a panel of cytokines being tested against the organoids that were vaccinated, and the differential cell responses are being characterized.

And here this is just a drill down into one of those wells showing that interferon beta, as expected, stimulates the response. And with that, I will take your questions. Thank you.

Sam Raney: Thank you so much. So I have a question for our panelists.

Panel Member: So you showed some IgM responses and T cell responses to strong agonists or to strong antigens. Have you—do you have a sense of whether you can detect IgG responses? How long can you keep the model? Can you look at switching?

David Brahney: Absolutely. Sorry, I rushed through it. So the naive response to the yellow fever vaccine shows the IgM response. And then it does convert, and the conversion is different. I apologize, but yes, these are IgG responses to the influenza, and yes, Mark's lab has shown that they get the full class switching.
So these recapitulate, as far as I can tell, and this is what he tells me, the full immune response as you would see in a human.

Panel Member: Maybe I can ask a quick question. Because you are showing that it could recognize response to very strong stimulus. But we are here discussing ability to form a generic product that is primarily very, very pure, and every bit, maybe, of something. So is your assay sensitive enough to tell anything about it?

David Brahney: That's why we need FDA support.

Sam Raney: Well, exactly. I think it's clear what the research there that's needed. Thank you so much, David. And we can perhaps revisit this during the panel discussion.

Our next speaker is Dr. Ravi Shankara from Sun Pharma.

Ravi Shankara (Sun Pharma): Thanks for providing an opportunity to present immunogenicity assessment of peptide products. It's a hot topic.

This is the disclaimer. Whatever we are saying is my own opinion, and not Sun Pharma's official views.

Regarding immunogenicity assessment, it's really well established. It's very much required because of the undesirable immune response, and the mechanism is well established with T cell and B cell responses and followed by T cell epitopes. Another important point is actually binding that needs to be that is really required in these situations, and at the same time for biologics. The ADA, we are measuring ADA, but for ANDAs, I mean for peptides, we are going through the ANDA.

Considering this, we have a clear-cut regulatory expectation, even though it is for only five peptides, it's extending to all other peptides. So I'm not going into detail on that.

As per regulatory recommendation, we have to perform innate immunogenicity as well as adaptive immunogenicity. Innate is with the whole product, and adaptive immunogenicity is initially with in silico, then followed by T cell binding and T cell selectivity. So while performing, a lot of challenges we are observing.

These are some of the challenges and recommendations where we need a guidance document to fasten this study because it's taking a lot of time. One is, we need a clear guidance document. And the second important part, I mean, probably these points can be considered to lay out guidance document. Second is length of peptide. What peptide we need to evaluate for immunogenicity, because it's clearly having a relationship with HLA binding with nine-mers.

And other important point is related to in silico assessment. In silico assessment we are performing, however, eventually we are ending with T cells. Then the question here is in silico assessment has any value addition, or we can straightaway consider it as a predictive tool rather than going ahead with initial experimentation part.

The most important point here is a lot of debate is happening on the concentration at what concentration we need to measure. So 0.5% is not acceptable. And there is a statement like concentration that ensures adequate presentation of the antigen presenting cell. It's really difficult to identify each and every impurity exactly the concentration. So generally, the expectation is more than 0.5 micromolar. It's nothing but 10 to 20% of the concentration.

The two-point series: How do we evaluate the concentration that ensures adequate presentation of antigen presenting cells? And the second part is there is a suggestion like we should go ahead with a 100% level. Is it realistic? Is a question mark where we need to have a lot of research.

And recent communication. Initially, we used to measure one marker. Now there is a recommendation for two markers. So the second marker should be clearly different, I mean defined, and looked into. The other important part is one of the aspects is innovator. If they're also having impurity, so it's a hypothetical case where the difference is less than 0.05%. But still we need to do immunogenicity. So the question here is how do we evaluate the innovator product in such situations?

That's one of the points where we need to go deep dive into that. And the second important point where I think FDA can look into is the type of product, because it surely determines the dosing frequency and the length of the dose. So it's short versus long term and dose content route of administration really matters to have triggering the immunogenicity response. So this is a very important point. And other couple of points like T cell numbers is very important. How do you have the minimum number of donors like more than HLAs is required.

Regarding innate immunogenicity, couple of points here are: There is no clarity on the selection criteria of the donors, so that should be looked into, and the cell viability in terms of PBMC versus subtype population viability.

And most important point here, like our previous speaker has touched upon, is the response, and Andrew is also stating the right thing. So the cytokine response, like if you observe at one

picogram as my LOQ, and your RLD provides the same thing, and generic product gives the 3 pg, so is it clinically relevant, even though it's a statistically significant? So clinical relevance establishment is much required for innate immunogenicity assessment.

The other most important point is excipient interaction. So I'm going ahead and, like the previous speaker also touched upon, synthetic peptide is really required to go ahead for immunogenicity assessment.

These are the recommendations for collaborative studies. One is, we can straightaway—we know the probable impurities, I mean formation of impurity. So in silico immunogenicity assessment can be conducted by the agency. Second is, we have commercially available impurity standards, so T cell proliferation of major impurities can be assessed.

And so I touched upon the clinical relevance. And best method can be in silico for what we need to have to remove the excipient interaction.

So I'm just touched upon—we need a decision tree. So I tried to prepare a decision tree. You can consider this very, very preliminary, and which can be debated a lot, and finally concluded, because it's very much needed to reach out for a submission perspective. So this is for adaptive, and this is for innate, which is very, very complex. A lot of things need to be evaluated here. With that, thank you very much.

Sam Raney: Thank you. That was a fantastic presentation. I think you articulated a lot of the uncertainties from an ANDA applicant's perspective in developing these products. Is there any quick questions? Otherwise I think we may have to come back at the panel discussion. Any quick questions from the panel?

Nope, okay, very good. Thank you so much.

Our next speaker is Dr. Marina Juretic from Pleva.

Marina Juretic (Pleva): Thank you for the invitation today. The topic of my presentation will be development of bio-relevant and bio-predictive in vitro release tools which would accelerate development of generic long-acting injectables for intramuscular and subcutaneous administration.

One of the challenges in generic LAI development is very long duration of bioequivalence studies, where often more than one BE study is needed, which increases patient burden in the studies and also prolongs LAI development.

Reason for failed BE study is primarily that we lack the knowledge of all of the formulation attributes which affect in vivo performance of LAI. Therefore, we are faced with a situation where in vitro, we see differences between test and reference product which may seem small or insignificant. However, after injection of formulation into the tissue, these differences may become critical and lead to difference in drug release and in vivo performance.

Therefore, we believe that bio-relevant IVRT mimicking injection sites and with the ability to predict in vivo performance of LAI would help us elucidate these critical formulation attributes, and in that way help us select a test formulation for BE study which would accelerate the overall generic LAI development.

So what are the physiological and anatomical aspects at the injection site which influence in vivo drug release and performance of LAIs? In short, for both administration routes, formulation is injected into the extracellular matrix at around 37°C. It is exposed to very limited volume of interstitial fluid of pH around 7.4, which contains different ions, but also proteins. And lastly, there is potential inflammation response.

As part of previous GDUFA research projects, a lot of papers have been published which developed IVRT methods for different LAIs. However, all these methods applied non-physiological hydrodynamics, non-physiological large medium volume and composition. The only physiological aspects that were mimicked were the pH and temperature.

For some of these methods, bio-predictiveness was demonstrated despite the lack of bio-relevance. However, this may be valid exclusively for this specific formulation type and API, and thus it cannot be applied universally to all other LAIs.

So why do we need to incorporate bio-relevance to establish bio-predictiveness of the IVRT assay? These illustrations demonstrate some of the phenomena which are taking place at the injection site and influence drug release, but are missing in standard IVRT setups.

For example, for suspensions in typical in vitro setup, both drug particles and excipients are freely dispersed in the medium, while at the injection site drug particles segregate and excipients are potentially retained, which influences drug release.

For gelling formulations, in in vitro usually depot is formed of uniform shape, and it can freely swell, however, at the injection site more irregular and variable depot shape is formed with very limited depot swelling.

And for polymeric microspheres and implants, there is a known phenomenon of acidification as a result of polymer degradation. However, this may be attenuated in in vitro setup due to high buffer capacity and large medium volume.

So to conclude, what we propose is that in future GDUFA program research is implemented which would develop a bio-relevant IVRT assay which mimics critical aspects of the injection site for drug release and is thus bio-predictive. This tool would help us select and more efficiently develop a test formulation for BE study.

The tool is not expected to be used for quality control purpose due to higher complexity. However, we believe that QC method may also benefit from the knowledge gained from the assay. And regarding the inflammation response at the injection site, we believe that other tools, such as cell-based or tissue-based, may be more appropriate for this purpose. Thank you all.

Sam Raney: It was excellent. Thank you. I think the point came across very clearly about how important it is to have the bio-relevance of the bio-predictive assays. I would ask some of our other industry colleagues who may also be involved in developing LAIs: is this something that resonates with you as well?

Panel Member: I would say yes, because there are differences in hydrolysis of, let's say, lactic glycolic polymers in vivo. So usually the hydrolysis is faster. So if we have a test, especially if you go out to longer periods of time, I think that would get us closer to testing what we'll see in clinical trials.

Sam Raney: And from our FDA colleagues, any comments?

FDA Panel Member: That was a very interesting presentation. Thank you. One of the issues we've seen with some of the skin or subcutaneous-based type assays is that immune cells are often lacking. They tend to wander off the tissue preparation. Have you considered that? Do you have a way of addressing this?

Marina Juretic: Sorry? Can you repeat the question regarding these models which mimic the subcutaneous?

FDA Panel Member: Have you considered whether it's important, or whether you need to have immune cells stay in the preparations for them to be really an adequate model, so that you have sort of a whole picture of what happens when you put in the product, the inflammation that surrounds it, etc.?

Marina Juretic: Well, as I emphasized at the end, immunological process is a very complex process, and we do not expect this process would be incorporated into this assay. Our view is that the assay would probably include the simulation of the extracellular matrix, its composition, and its properties because it interacts with the formulation in that way affects the drug release. Immunological response may be evaluated, but with some another tool, for example, cell-based or tissue-based. But this is a very complex area which needs additional research aside from development of this bio-relevant assay.

Sam Raney: A quick question.

Panel Member: I'll just throw it out there, and we can continue to discuss. So when you talk about IVRT, I think the general challenge is even for the same formulation, it's very condition dependent. So when you see bio-relevance, do you think is more important in terms of the composition of the media and the volume and the hydrodynamics versus really understanding what's going on in terms of the mechanism theoretically and then trying to reflect that in vitro? So I think it's actually a big question we can continue to discuss.

Marina Juretic: Yes, I agree. Thank you.

Sam Raney: Wonderful. So we'll flag that for a revisiting during the panel discussion. Thank you so much.

Our next speaker is Itay Spicher from DGM.

Itay Spicher (DGM): Thank you for inviting me and DGM to present our technology to promote generic drug approval. My name is Vitas Pater. I'm the director of business development at DGM. I'm very excited to be here and present our technology to promote generic drug development.

One of the challenges with generic development is the long testing cycles that these products tend to have. Once a few formulations are being selected, they're being tested, and then based on their performance, they're being tested again. And then this cycle repeats, and this cycle repeats in many stages, including manufacturing and different QA and QC environments, as you can see here in the slide.

The added total cost of these testing cycles often creates a huge bottleneck from the industry standpoint of material availability, tech transfer activities, as well as ensuring product performance.

And what does it mean for our generic clients? So with generic development, they face a very similar situation, and to add to that complexity, they're already operating in a very competitive and complex environment, and to add to that, they need to often guess the RLD structure and performance, and that can be a very timely and costly endeavor, which sometimes basically causes them to cease activities altogether. And this is where we're trying to really help them with our solution.

So our solution to that is really called DG Map, and it starts with characterizing the RLD, and we use a combination of high-resolution imaging modalities. One of them, as you can see on the screen, is called focused ion beam scanning electron microscopy. And this is an invasive technique where we are assessing the internal structure of a single microsphere, where we are assessing the particle size distribution of the active as well as the porosity and the PLA matrix. And we often complement that with a 3D non-destructive X-ray microscopy technique to basically assess batch-to-batch homogeneity.

And that's basically creating a digital twin of the actual drug product. And once we have that understanding, we can then compare the few selected in-house test formulations to compare to see how they match versus the RLD. And because we have the digital twin, now we can ask ourselves "what if" questions. So what if we change one of those key attributes that we found from the first step? How does that affect product performance?

And we can do that all experimentally, basically in silico without creating a physical product altogether. And once we have that understanding, we can then agglomerate all this data together, and we often help our clients by submitting all this information, the microstructure equivalence data to support ANDA packages.

So the FDA is very clear in its intent to reduce the amount of testing that is being done and also reuse data and refine it. And this is exactly what we're doing here. So often when we engage with projects with our clients, this data is not getting lost. So in this example, we created a web-based app, as you can see there on the left, at the request of the FDA, based on literature data where this basically helps predict drug release for a combination of over 30 different API and polymer systems. And that's something that we often do. We take microstructure data that we created, combine it with microstructure data that our clients have, and together with literature data, we basically create a complete product that we can deploy at our customer sites to facilitate better communication and bridge gaps in knowledge between different teams in the organization.

So to summarize the work that we have done to date, our work spans across different dosage forms and delivery systems. So this slide basically summarizes the number of projects that we worked on over the years. And basically, we're very excited to continue the work that we are doing with the FDA and our other generic clients to promote and accelerate generic drug approval. So with that, I'll be happy to take any questions and thank you very much.

Sam Raney: Thank you so much. I think obviously very powerful technology. I think part of the question may be, though, of all the things that you could do with it, what research would be appropriate to prioritize that would be most useful for the generic drug industry?

Panel Member: I would like to ask a question to Itay. So is it really limited to PLA-based, or can you also develop some in silico modeling for different high molecular weight or molecular polymers and some different polymers that can be used in transdermal products, too?

Itay Spicher: Yes, so we've worked with other polymer systems. We work with PLGA, we work with other polymer systems. And we have in silico modeling approaches based on diffusion, based on erosion. And we take into consideration different molecular properties.

Panel Member: So how is it evaluated in silico exactly? If you have to validate the model?

Itay Spicher: So we publish papers with the FDA and we publish papers with Purdue and Lilly, and we saw a great agreement with in silico and in vitro and in vivo data. This is still ongoing research. But yeah.

Panel Member: I think your research is really very—this should be prioritized, I believe.

Sam Raney: Thank you. Perfect. That's exactly what we're here to figure out. Thank you so much Itay. And we'll revisit this for the panel discussion.

Our next speaker is Dr. John Lenn from MedPharm

John Lenn (MedPharm): Hi! My name is John. Thank you for having me here. I'm going to switch gears a little bit and talk about the chemical stability of benzoyl peroxide and the potential formation of benzene in complex formulations like topicals. It's an old drug with a potential new problem.

For those of you who have worked with benzoyl peroxide, you will know that it's an inherently unstable molecule. Most people that work with this molecule are primarily focused on looking at BPO and an end product which is benzoic acid and a few intermediates in between. Very few, if any, people are looking at benzene in this process.

There's a lot of effort and work done to stabilize BPO. Most of that work is done on the formulation to try to prevent that degradation. It's unique where it's one of those molecules where you want to keep it in suspension to prevent that degradation. Packaging is certainly a big part of that, and temperature also has an impact. There are both prescription and over-the-counter products here. A lot of the prescription products will do things like cold chain storage to minimize that degradation.

Any of you that have kids or have had acne, you've used it. It's very widely used. It's probably one of the most commonly used actives in mild forms of acne. It's used in children, teens, and adults. So there is a younger population. So there's a risk-benefit scenario here that I think is very important to this compound. Again, it's developed both on the prescription side as well as OTC. Generic companies have a lot of these products as well.

There is a recent citizen's petition on BPO, which caused some questions. A lot of that data suggests that there's the potential to form benzene. However, a lot of that data looks at sort of accelerated temperatures and conditions that are way outside of the package recommendations.

However, there is some data in there to suggest that benzene may be formed or forming at room temperature within the package inserts. Benzene is known to cause cancer. And there's some recommendations on how low you can have that around 2 parts per million. Social media got a hold of that and created a lot of questions, a lot of concerns. Those are coming from patients and physicians. I've met with some dermatologists, and they don't really know what to do. There are the extremes where they're saying, don't prescribe it, don't use it. There are some people in the middle who are saying, just put it in the refrigerator. And so that's created this big question.

That's why I'm here today to propose some research on this to figure out, is this a problem? How big of a problem is that? And what are the acceptable levels of benzene? And this all starts at the product level. Measuring within that package recommendation: Is there the presence of benzene? And how long over that shelf life?

Analytics will be something that we need to look at. Given the selectivity and the sensitivity issues with this specific compound and the degradants, it's also very complex. So as you extract out the BPO from the product, you can actually generate benzene. So there's some questions on validation of the extraction methods, and how you do that. Temperature and humidity, as I've said, is a big part of that. And so, looking at where are the extremes? And where do you set those boundaries?

Again, that will apply to all products, even current products and any new products. There are monographs out there, however, none of those monographs include the analysis of benzene.

Another area of focus is to the consumers and the use of BPO products. Does it really increase your person's—that person's risk of cancer? And that's one of the questions. Certainly there's some education that needs to occur with the safe use of these products and adhering to these package labeling.

There are some things that we can do, I think, relatively easily. These are established assays that we use commonly in the generic space. In vitro release testing is one sort of a worst-case scenario. So how much benzene is getting released out of that? Again, appropriate validation of that to make sure that you're not introducing artifacts. And then in vitro permeation testing which uses human skin. That's sort of more of a best case with an effective barrier. So that will look at how much of that compound gets into and through the skin, looking at the kinetics.

If we do want to start looking at tissue and blood levels, you can certainly move into traditional PK studies either in animal or humans. And then again, characterizing those temperature fluctuations that are far outside of the package recommendations. And then there's the full, outstanding question of health literacy and how do we educate the population, the public that these package labels are there for a reason. And when we're outside of that, how much concern should you have?

Sam Raney: Thank you very much. I think a very clear presentation. You know, I remember it harkens back to when we had presentations a few years ago about nitrosamines. And I think one of the biggest questions that I would have for our industry panelists and then for FDA panelists as well: How concerned are you at this point about what benzene and benzene impurities might mean for your products going forward?

Is this something that you're quite concerned about? Is this an area where you feel that FDA should be investing some research?

And then I'll offer our FDA panelists a moment to comment on that as well.

Then maybe if John, if you can comment a little bit on how widespread a challenge, do you think this is going to be in terms of benzene impurities.

John Lenn: Well, I mean, I know that we spend a lot of time developing products and stabilizing BPO. Certainly we don't look at benzene. We don't measure it. We don't quantify it. We're primarily focused on benzoic acid. So this is sort of new to us. We have started doing some research on products. And it is there. And it's sort of like, do you want to open that? And then my biggest concern is the package labeling is there for a reason, and developers do that, and that's what the product should be stored at. And so then, if you vary from that, I think you create a problem across products.

Sam Raney: Okay, well, thank you so much for coming and speaking with us about that.

We'll now proceed to a couple of virtual presentations from Prof. Conor Evans from Harvard Medical School and prof Matthias Wacker at the National University of Singapore at

Conor Evans (Harvard Medical School): Hello! I'm excited to share with you collaborative work my team at the Wellman Center for Photomedicine, Massachusetts General Hospital has been carrying out with the FDA in developing a new toolkit for topical product bioequivalence known as pharmacokinetic tomography.

In order to measure bioequivalence, we need to measure permeation. The flow or flux of a drug within tissue. This is challenging for topical products. There's a lack of methods to directly follow the permeation of APIs on the microscale in skin. There are radiographic methods that can tell you uptake—these don't give you dynamics. Modifying small molecule drugs by fluorescence often fundamentally alters pharmacokinetics. And while there are sampling methods, including tape stripping, dermal microdialysis, and dermal open flow microperfusion, these don't provide microscale information, and many of them do not provide epidermal information.

So there is a gap in our understanding of drug permeation within skin and our ability to then calculate topical product bioequivalence.

What we have been developing is a toolkit known as pharmacokinetic tomography, which is a paradigm for microscopic imaging of drugs based on intrinsic sources of contrast. And by intrinsic, I mean presence and molecular structure. We can actually directly image molecular structure, or the concentrations of molecules by their molecular structure, by tuning in like a tuning fork into molecular vibrations that are inherent in molecular structure. We can do this through a toolkit known as stimulated Raman scattering.

These enable direct imaging and quantifications of APIs within skin via their inherent molecular vibrations.

As an example of this, I can show the measurement of epidermal pharmacokinetics of the API ruxolitinib. We can take our imaging system and tune into lipids by tuning into their CH stretching vibrations, and we can tune into the drug, the API in this case, through its nitrile vibration.

When we apply the drug to the skin initially, we don't see any deposition, and we only see the red lipid distribution on the surface of the skin. But after 70 minutes and 120 minutes, we can see that this API deposits on the skin and permeates through the epidermis. We can see it colocalizes with lipid-rich spaces, and we can also determine that it forms depots which it permeates into skin.

This type of data can be quantified by image analysis and calculated into pharmacokinetic parameters.

Working with the FDA, we utilized pharmacokinetic tomography with SRS imaging in order to compare the permeation of APIs in the epidermis of ex vivo human skin across different topical products. Here, showing data for tazarotene products, we looked at the reference drug, a generic cream in the same format and alternative gel format, and a lab-made formulation, and then looked at parameters such as Tmax, Cmax, and AUC calculated from the microscopic images.

The reference product was replicated, allowing us to look at experimental variability. We can see from this data that the Cmax values, when compared, are similar for the generic and the reference drugs, but are different for the alternative formulations, both in terms of Cmax and AUC.

Using both FDA guidance for IVPT studies as well as nested linear mixed effects analysis, we can compare these pharmacokinetic parameters between different products—the reference, generic, alternative formulation, and the lab-based formulation—to see whether the topical product falls within the FDA recommended 90% confidence intervals which would classify it as being bioequivalent.

We can see for this data that the reference against itself is bioequivalent. The generic is bioequivalent, and the generic gel is bioequivalent. But the lab-made formulation falls outside of these areas indicating it is not bioequivalent.

We have continued these studies in other formulations, other APIs, and are continuing to develop the technology towards in vivo pharmacokinetic tomography in healthy subjects as well as in the future disease subjects, so that we can calculate bioequivalence in these critical individuals and understand how to improve our production of generic drugs for patients.

Matthias Wacker (National University of Singapore): Hello, and welcome everyone. My name is Matthias Wacker, and I'm very happy to speak here today at the generic drug science and research initiatives workshop.

Today, I will emphasize complex injectables and why we really need to understand drug delivery in order to make better predictions. Let's go.

If you want to learn more about our research, you can also visit our website using the QR code, or you just go to www.wackerlab.com.

Let's begin with long-circulating liposomes, the topic we began exploring a few years ago. If our topic is to create safe-by-design nanomedicines, we need to discuss IVIVC. The good news is it's achievable. I will use liposomes as a reference point, mainly because most of the translated nanomedicines are indeed coming from this platform technology.

One of our recent publications details the development of such a bio-predictive method, including the extraction of the zero-order release that is an equivalent of the absorption kinetics from nanocarriers. Also, it explains the in vitro release test method that we used and a few mechanistic considerations. Those include, for example, the selection of the release medium. Ultimately this led to a meaningful IVIVC.

We opted for a model-based deconvolution to extract the absorption kinetics. A traditional PK model would just not do. Fortunately, we had developed a convolution model about four years ago that perfectly met our needs.

For liposomes, many release test methods are described in the literature. However, there's a general lack of good standards and technical limitations often also limit our understanding of the release process. This is the one that we use in our lab, and we are actively working towards those standards.

Here, you can gain a bit more insight into our methodology for IVIVC development. We think that rodent data is inherently limited. That is why we chose to use only human data from human clinical trials conducted with Caelyx, which is the European version of Doxil, Lipodox, which is the Sandoz version generic of Doxil, and Thermodox, which is an improved generic.

Those three different formulations were tested in our release test method. And here you can see the outcome of our IVIVC development. After optimizing the medium, we got really an excellent prediction. What we could show here is that predictions without the presence of plasma or serum are not really meaningful. The full story you can, of course, read in the paper, but that is the very short version of it.

One big issue in the development of liposomal generics is that we must have a good understanding of how representative the plasma PK really is. Our PB model uses two parameters to estimate the risk. Those are the carrier half-life and the in vivo release. They actually tell you the percentage of the drug that is found in the plasma. When we look at the release profile, this is the percentage released. On the other hand, we also see the leftovers—whatever is accumulated somewhere in the periphery and will probably be released somewhere else.

This very concept of a model-based deconvolution we implemented into our virtual risk estimation framework and sustained our findings with tissue distribution data from rats. On the left you can see the plasma levels of the drug illustrated with different colors. Lighter colors means that the drug was completely observed in the plasma, so we monitor it very accurately. However, darker colors indicate that the drug ended up somewhere else where we cannot really capture it.

This leaves us with a very simplistic risk estimation. We have the long plasma circulation half-life of the carrier, but the fast release. That means that the exposure is mostly covered by our framework. Then we have the short plasma circulation. Those have stronger interactions with tissue and the fast release. Those formulations come with an elevated risk. Then we have the long plasma circulation half-life and slow release. Those come with a slightly higher risk. And finally, we have the high-risk category: short plasma circulation half-life and slow release formulations.

Interestingly, solid lipid nanoparticles, one of the newest formulations, fall into a higher risk category.

So what are the research needs of tomorrow? We have to advance PBB modeling to enhance the predictive accuracy, but also to replace animal testing in the future. We must develop data-driven risk assessment tools that leverage existing data pools from previous generations of drug products. And finally, we must establish robust testing protocols for performance validation of complex injectables.

I will talk about more examples during the panel discussion. Here you can see my team, and I hope that we have a fruitful discussion. Thank you very much.

Sam Raney: Thank you to our virtual presenters.

So that concludes the first segment of this public comment session. We're not stopping, though. It concludes it thematically because these were talks that were focused on research on characterization methods for complex products.

We'll now be transitioning into more talks on oral dosage forms and some complex issues relating to these dosage forms. Please join me in welcoming Professor Mark Taraban from the University of Maryland, who will be our next public comment speaker.

Mark Taraban (University of Maryland): Good morning, and thank you so much for this opportunity to present our results and our thoughts on the possibilities. I'm here representing the University of Maryland School of Pharmacy. But physically we are located at the Institute for Bioscience and Biotechnology Research. It's a joint facility between University of Maryland and National Institute of Standards and Technologies.

Today I want to introduce one very simple technology which is called benchtop NMR relaxometry. It's a non-invasive and fast analysis of drug products. And to preempt the questions from those who are very much familiar with the nuclear magnetic resonance technology: No, we are not using NMR tubes. We are not using deuterium as the lock standard. Our instruments are benchtop NMR relaxometers with the wide bore that allows to accommodate the drug product in their original container without taking out something, without opening, and after measurement the drug product could be further used for patients or for any other uses. You can see this instrument that allows you to accommodate insulin pens, big vials, closed vaccine vials, and measurements are very fast and allow to characterize the product.

Here is the benchtop NMR facility at the IBBR that hosts four different instruments. Our technology has been already approved and tested for use for pharmaceutical drug products, such as monoclonal antibody formulations for their concentration, aggregation, content for vaccines, counterfeit and stability studies for gene and cell therapy products.

Our group holds more than 40 different publications in this area of applications of water proton NMR relaxometry and more than 15 patents in this area.

But today I want to point out several interesting topics that we consider to be useful for studying the generic drugs. First of all, it's a capability to study variability between brand and generic drugs for liquid formulations. It will reveal the differences between brand and generic, and compare the variability of both of them. We already have demonstrated this for insulin innovative products and follow-ons, and we also have demonstrated this for filgrastim as biotherapeutics.

For solid formulations, this technology will provide accurate evaluation of different contributions of the morphology of the sample and the content, like crystalline, semi-crystalline.

And second, that we think it will be useful is dissolution kinetics comparison for brand versus generic. In this technology, we can provide values of dissolution rate constants or dissolution rates and could be performed at different temperatures, different media and different volumes with data collection. Increment might be from seconds to minutes.

And for lyophilized powders, we also can use this technology for the dissolution kinetics to see the reconstitution of the lyophilized drug, and how it goes, and all the constants there.

Thank you for your attention. And this is the information or contact information if everyone is interested to collaborate with our group.

Sam Raney: Thank you so much, Professor. There are some broad applications for benchtop NMR. Are there some specific challenges for generic product development that you think should be prioritized? And is there specific research that you think should be prioritized to address those challenges?

Marc Taraban: Well, we are not involved in the development of the products, but we might be capable to provide precise analytical information when this development goes on. So we might be able to distinguish between different properties of generic and brand products, using this and help people who are developing this and help people who are approving this to see the differences, how different these products are, and whether this somehow affects the bioequivalence properties, or other properties.

We need to have a collaborator to correlate our results. But in general, relaxation rates of the products are very sensitive to any tiny changes in the structure, any tiny changes of the contribution of different components there, or crystalline or semi-crystalline in solid formulation.

Sam Raney: I'll open the panel to comment on whether this is research that would be helpful for FDA to prioritize.

Panel Member: I just want to comment. This would certainly benefit in terms of how user-friendly it is, and how easy it would be to analyze. But just in terms of NMR has very wide applications. So would you think it would be sensitive enough to go to the structural level like the primary structure level for peptides?

Marc Taraban: So this technology, of course, is not providing with the defined structural information, but any structural changes results in the changes of their relaxation rates. For example, if you have a protein aggregated, a protein distorted structure, that's immediately reflected on the relaxation rate of the media because of the permanent interaction between media and the solutes or the protein itself. So you won't be able to figure out what happened. But you definitely will see the change that something has happened. The structural changes happened.

Sam Raney: Thank you. Any questions from our panelists? If not, thank you so much. And we'll look forward to revisiting this during the panel discussion.

Our next speaker is Dr. Grzegorz Garbacz, I apologize, I am certain that I did not pronounce itproperly, from Physiolution.

Grzegorz Garbacz (Physiolution): Slavic names tend to be difficult in pronunciation. So thank you very much. Perhaps you could introduce yourself. My name is Grzegorz Garbacz. I came all the way to you from Poland and Germany. I represent Physiolution, which is a company specialized in the bio-predictive testing of oral drugs.

In the next couple of minutes I will tell you more about the bio-predictive testing of oral drugs and how to do this in the physiological design space.

Our goals for the development of the work that I will be presenting today was to develop methodology for the simulation of the individual variability of the fasted stomach in an informal in vitro test protocols that could be useful for the characterization of oral drugs of immediate release.

And the second goal for the development was to generate navigation of the dissolution profiles for the individual simulated gastric conditions within the physiological test space in such a way that we can reflect the variability range of the drug delivery performance of the formulation in vivo.

So I would like to show you the way of thinking or the way of working, based on the results, on practical results, that we clarified over the last months.

And this is the same drug which is given as pellets or pellets that are filled in capsule. The pellets contain only weak base API and enteric core. When we give the pellets in form of capsules to our fasted volunteers, we observe very high variability of the drug plasma levels, and we observe quite long Tmax of approximately 2 hours.

If you compare this to the bare pellets, you will not—I stop giving the bare pellets—so same formulation, but without the capsule shell, you can achieve significantly higher AUCs and significantly higher Cmax. And the difference is only the formulation, but the capsule shell.

So how to test such a formulation, or how to clarify such case, you need to specify the physiological parameters of interest that can affect the drug delivery performance of the formulation. Among others, you will find here gradients of temperature, gradient of emptying rate of stomach, the magnitude and the intensity of the intragastric pressure.

And you will find here also factors that are affecting the dissolution performance of dosage form. Mostly, these are the gastric pH range, which can vary between 1.2 and 4.0, the timing of the intragastric stress which, according to our data, our knowledge ranges somewhere between 5 and 40 minutes, roughly, and timing of the gastric emptying of solids.

Having such data or having such information on the physiology of the human gastrointestinal tract, you are able to develop a three-dimensional design space which covers the variability range of the parameters of interest in vivo.

And within this design space depicted here, you test the dissolution performance of your dosage forms.

How to test to mimic such conditions? You need simple, reliable tools that are able to give you reproducible results over time. And for this purpose we developed a concept which is called Physiodissolutor, and the Physiodissolutor allows us to simulate different gastric emptying kinetics of water, different temperature of the dissolution media, different pH, and also in the flow-through cell we placed an elastic sleeve which is given here, and by contracting this sleeve we can squeeze the dosage form with some mechanical pressure of preselected, predetermined magnitude and duration and intensity.

This allows us to simulate intragastric conditions to which the dosage form is exposed.

And having such a tool, we started to characterize the pellets and capsules separately, and the pellets are always given us the blue line, the capsules are always given us the orange one.

What we can observe here is that in the experiments that we performed, the pellets were unaffected by the mechanical agitation which is depicted by the dashed lines, and that the pellets dissolved very rapidly, and dissolved completely under the simulated gastric conditions, whereas the capsules were extremely dependent on the mechanical agitation in the stomach, or in the small intestine, and only partially delivered the material.

So in the variety of the dissolution profiles that we collected, we specified models, mathematical models for depicting the drug delivery performance of the formulation within the physiological design space.

They allow us to describe the dissolution behavior of the formulations. We verified such models, and we use them to ask the "what if" scenarios. So it allowed us to conclude experiments under conditions that are not within the set of learning data and to create family of dissolution profiles.

So the add-on value that the machine learning brings is the simulation of the determination of the dissolution, the local effects of pH and precipitation. We can evaluate the impact of the gastric motility. And we can understand the physiological parameters that impact the drug delivery performance.

The machine learning modeling allows us to investigate the conditions under the—a process. But better to understand the conditions in the experiment, we are able to cover the relevant physiological factors.

And we can, for the first time ever on the experimental level, be capable of capturing the intra-individual and inter-individual variability of the gastrointestinal parameters on the drug delivery performance of the formulation. And this we can do in the preclinical stage.

And by this I would like to finish. Thank you.

Sam Raney: Thank you. So I think the rationale of the approach was clear in terms of the specific challenge for generic product development or assessment that you think this would address. Are you able to comment on that?

Grzegorz Garbacz: Yes. Well, so from our perspective, the key factor is to develop bio-predictive methods and focus on the variability range of the physiological parameters. So today, I've shown you only a small piece of our work which concerns the intragastric conditions, how variable they are! And how can we describe them, based on semi-empirical models that we developed during the rational characterization?

And I think this brings a lot of understanding of the formulation properties, and allows you to understand the formulation much better before you will enter the clinical trial. And I would even go a little bit further. So, having the rationale for the testing of the dosage forms and having good, simple, and straightforward bio-predictive tools, you are able to develop models to describe the variability of the formulation that can be expected on the application side, and having such data, such rational physiology-driven input function, you are able to mimic the pharmacokinetics of the study groups.

You can mimic the cohorts. You can predict the outcomes of the clinical trials. And that's this is the real benefit. Because you understand the development process and the formulation properties throughout—it starts from the formulation level until you end up on the level of clinical trial.

Sam Raney: just very briefly, any comments from our panelists?

Panel Member: Hi! I have a question. So in your third block, you have a model to predict the dissolution profile, and on the fourth block you have another model to predict the PK profile based on the dissolution profile. Each model has their own errors. How you control, I mean, can you share some insight how you control the integrated error?

Grzegorz Garbacz: So it starts with the model verification of the dissolution model. So you can describe the drug delivery performance using the so-called bio-predictive, bio-relevant dissolution space or variability space. And then you verify the outcomes of the predictions which are given us the red lines, and you compare them to the outcomes of the numeric simulations which are given us the blue lines.

You determine the percentage of the data points that are covered by the results of the simulation. And what's important, or what's even more important, you compare the shape or nature of the profiles that you generated. The drug delivery performance is all about the dynamics. So you need to reflect the shape and the dynamics of the drug delivery performance of the formulation on both experimental and prediction side of the story.

This allows you to believe that you have a tool which is capable of generating reasonable drug delivery profiles that can be subjected to any kind of numeric simulations of drug plasma levels. And from our perspective we are using very simple mechanistic models. And by having a rational input function for the simulation, we are able to generate valuable data.

Sam Raney: Perhaps we can revisit this during the panel discussion, just to be respectful to the next speaker's time. Thank you so much.

Our next presenters in the series are virtual presenters. The first one is Professor Tao Zhang from SUNY Binghamton.

Tao Zhang (SUNY Binghamton): Good morning, everyone. Thank you for this opportunity to present research on developments and assessment. I'm from the Department of Pharmaceutical Sciences at SUNY Binghamton University. The topic I'm going to present is food effect on oral extended release products supported by our research.

Firstly, I will provide a brief background introduction for the modified release formulations. Modified release formulations are an important class of drugs on the market. From 1998 to 2021, about one quarter of the oral drugs approved by FDA were MR formulations.

Modified release formulations include the delayed release formulations, oral disintegrating tablets, extended release formulations and ER, and IR combination formulations. Our focus research here will focus on ER formulations because they share some common characteristics that warrant further investigation to support the generic drug development.

Currently, according to M9 guidelines, a clinical food effect study may be waived for all immediate release formulations of BCS class one drugs. However, for all MR drug products, food effect study should be conducted.

Nevertheless, a recent publication by our group, Dr. Zhang, has shown that more than half of the ER products do not exhibit any food effect under fed conditions. This finding prompts us to further explore the mechanism of food effect on ER drug products.

Now let's consider major physiological changes which include the migration of MMC, increasing gastric and duodenal flow, etc. Most of these changes are transient and last for approximately 2 hours.

For most ER products in which drug release is limited to less than 20% within 4 hours post-dose in a fasted state, ER tablets can arrive at the ascending colon as early as 3.5 hours post-oral administration. Therefore we can infer that ER drug absorption under fasted conditions may primarily occur in the colon and rectum. In contrast, in a fed state, it takes over 6.5 hours for an ER tablet to arrive at ascending colon. Clearly both the small intestine and colon significantly contributed to drug absorption.

Understanding drug absorption in the human large intestine is equally important as small intestine for predicting food effect of ER products. However, the development and validation of reliable tools to predict the colonic absorption of ER drug products has been limited.

In recent years, the use of mechanistic PBPK modeling and simulation to support regulatory decisions and generic drug development has been endorsed by FDA Office of Generic Drugs. However, many of the published models hopefully by prediction were developed for specific drug products and are building scenarios with optimized parameters considered only for use for them.

Therefore, more research is warranted to develop a consistent and reproducible in vitro assays with input to extrapolation to PBPK models to fill this knowledge gap.

To address this need, in collaboration with Dr. Zhang and Dr. Lee, we propose to include in vitro and in silico PBPK modeling and simulation to predict the food effect of oral ER drug products.

We will develop colonic in vitro assays and build PBPK models with more focus on colonic absorption. The intent is to identify crucial physiological and population parameters that have the most impact on food effect of ER drug products.

The completion of this project will provide insight and may help establish criteria for regulatory decision-making regarding when biowaiver studies for oral ER products. We sincerely welcome the comments and advice from the experts here. Please feel free to send us any questions.

Sam Raney: our next speaker will be Professor Hannah Batchelor from the University of Strathclyde.

Hannah Batchelor (University of Strathclyde): Hi! My name is Hannah Batchelor. Thanks for the opportunity for me to present today.

The critical element of this work addresses the need for better predictions of bioequivalence for generic products in pediatric populations. Evidence of inequivalence has previously been highlighted in the literature, such as the papers shown here.

And the goal here is to develop methods that can accurately predict bioequivalence in pediatric populations using in vitro and in silico methods.

The proposed research really explores the elements of the formulation in predicting product performance, using bio-predictive dissolution methodology in conjunction with PBPK modeling to really understand and de-risk products in pediatric populations. These, in combination, are a really powerful tool that we can use to undertake virtual bioequivalence studies, minimizing clinical studies in pediatric populations.

Using dissolution to predict bioequivalence isn't new, and conventional dissolution has been used before, where we've considered the variability and composition and volume in GI fluids in children. However, there's an opportunity to use more advanced dissolution methodology going forwards.

This slide shows previous work using conventional dissolution. You can see different conditions were explored here, and the dashed line is showing the dissolution conditions that mapped onto the clinical data for a pediatric study using carbamazepine.

These conditions showed that a lower volume and composition, closely resembling pediatrics, was superior, thus indicating the need for bio-predictive methodology.

This slide is showing how valuable bio-predictive methodology is using the advanced dissolution apparatus. Here it's the TNO system. Correlation was developed for 19 compounds during the in vivo data and in vitro data showing the powerful predictions of this apparatus for formulations.

This is work conducted showing correlation values of 0.78, which is quite powerful as an IVIVC technique.

The use of dissolution apparatus in pediatrics isn't new. Previous studies have looked at formulations in pediatric populations representing neonates, infants, and toddlers, and rank order predictions were going to be valid for three different drugs within these populations. However, there's yet to be a more comprehensive study to really show the true power of this apparatus in this population.

Further work to just enhance the use of this has looked at food effects in adults and acid-reducing agents in adults. And again showing this really nice correlation between in vitro and in vivo data.

To incorporate the dissolution into PBPK modeling is really important. Currently, PBPK models cannot assess the impact of the formulation process changes or compositional variation. That's

an aspect that's really important for generic products, particularly when used in pediatric populations. This is the gap that this proposal hopes to fill.

This slide here is showing that the integration of data from such an advanced dissolution model really helps in the prediction of clinical pharmacokinetic profiles, and this is used for poorly soluble compounds in an adult scenario. Again, these are the more challenging products where we're more likely to have risks of bioequivalence in pediatrics. And these are the ones we really want to understand.

So the proposed research will really look at generating correlation between pediatrics and the in vitro model and validating that against clinical data.

We could then be integrating this dissolution into PBPK models, where you could look at an almost effective, safe dissolution space or clinically relevant dissolution space for pediatric products.

Then conduct some virtual bioequivalence studies to really minimize the risks of inequivalence in pediatric populations.

Thanks so much for the opportunity to present and for your attention.

Sam Raney: thank you. Our next speaker will be Dr. Joseph Al-Gousous from the University of Michigan.

Joseph Al-Gousous (University of Michigan): Hello, everybody! This presentation will be about bio-relevant dissolution testing for pH-independent delayed release drug products.

The most common type of such products is the enteric-coated dosage form that prevents drug release until after gastric emptying. Typically for protecting an acid labile API against gastric juice or for protecting the gastric mucosa against an irritant API.

They are usually based on methacrylic polymers that are unionized in the stomach but ionized and dissolve in the small intestine.

Now, the dissolution test for such products is typically the USP test, which involves 2 hours in 0.1 normal HCl to check the ability of the product to withstand gastric juices followed by 1 hour in 50 millimolar, pH 6.8 phosphate buffer to check the ability of the product to release in the small intestine.

The question is, how bio-relevant is this method design?

The answer is probably not much, as we see in this data, as recorded for aspirin at the London clinic.

Now the USP dissolution method gives an in vitro onset of release of around 15 minutes. However, in vivo, intragastric observation, GI disintegration for release until time of 1.1 hours post gastric emptying.

Now this is 15 minutes post, and this is 1.1 hours. Both gastric can be. That is a 4-fold difference, more than fourfold difference, which is much.

Why? Very easy seems to be the USP buffer poorly matching to the intestinal bicarbonate buffer in terms of buffer capacity, as shown by this data for the 325 milligrams enteric-coated aspirin tablets.

The green curve here represents the release in the USP buffer, which is quick, while both three curves represent their release under physiological upper small intestinal conditions, which are 5 to 15 millimolar bicarbonate. All the terms are under pH 6.8. Now, the typical bicarbonate molarity in the upper small intestine ranges from 5 to 15 millimolar. So this is a 15 millimolar, this is a 10 millimolar, and this is the 5 millimolar. As you see, the difference is dramatic between those three curves on one side and the USP buffer on the other.

And this is actually in line with the findings of some medical researchers that say that the majority of the cases of aspirin failure to provide adequate cardiovascular protection has to do with the failure of the enteric-coated dosage form rather than real population resistance to aspirin. That's why they termed this even pseudo-resistance.

And this brings us to the question which dissolution medium should we use? Now we could use bicarbonate, but it is technically challenging, due to the need of continuous CO2 sparging.

And this week we have successfully applied a mechanistic modeling-based target buffer design for small molecules that is to calculate, based on mechanistic modeling, which, for example, for aspirin would give us a phosphate buffer that drug and the dissolution performance of the drug that is similar to what the performance would be in bicarbonate. However, polymers are much more complicated than small molecules.

But we started first with an empirical design based on phosphate matching bicarbonate, then we moved to semi-mechanistic design mainly this capacity to achieve very good results. The next step would be a fully mechanistic design together with further validation with in vivo data.

And thank you for listening.

Sam Raney: thank you. Our next speaker will be Professor Emeritus Panos Macheras from the National and Kapodistrian University of Athens.

Panos Macheras (National and Kapodistrian University of Athens): Good morning, ladies and gentlemen. My talk today is about the applications of finite absorption time in various processes, phenomena of drug absorption.

This is a plan of my talk.

First, I would like to describe the work of Bateman back in 1910, when he analyzed this scheme. The isotope called Mother is decomposed to Isotope called daughter, and this is decomposed to Isotope called granddaughter.

He analyzed the concentration time profile of the daughter, and he derived this bi-exponential equation.

Many years later, Dost analyzed the GI absorption for drugs, and he found the same relationship by applying a very simple scheme, indicating the drug absorption from the GI tract follows first-order absorption.

All of us know these classical relationships, and we also know that there, AUC is the infinite integral of equation two.

As you probably realize, the infinite absorption time is irrelevant. There's no physiological meaning. And for this reason I wrote this commentary back in 2019.

Then we developed the concept of FAT, publishing this article, where you can see that the drug is absorbed mainly in the small intestine. When we have class one drugs, while for class 2, 3, and 4, we can also have absorption in the colon.

But basically, we have absorption for small intestine. We apply time limits for the absorption in the small intestine less than 5 hours and the absorption up to the end of the colon up to be 30 hours.

Then we developed the mathematics. Here is the relevant paper.

And we describe the absorption of drugs following passive absorption principles under sink conditions. Since the blood flow in the vena cava is too high, there is a presentation of three consecutive absorption phases.

Here are the equations, here are the differential equations. Here are the analytical solutions, simulations indicating very same profiles for one to three compartment model drugs. In all cases we define the duration of absorption for each particular stage.

There are fittings with our models describing the kinetics. Again, you can see the duration of two input phases.

How about we'll have the residuals profile.

There are so many examples we analyzed.

We apply this methodology for estimating the absolute bioavailability for oral dosage forms exclusively.

We also apply this for in the field of generics.

We revamped the basics, the roots of biopharmaceutics, and in particular the present absorption time curves.

The exponential profile we are familiar in all absorption studies in action. Practice takes place as a bilinear profile. Here are the Wagner plots and plots modified in terms of the FAT and the Loo-Riegelman plots modified in terms of FAT. Here are the results of the bilinear population. We utilize this concept and we revised the in vitro correlations. And, as you can see here we developed the Levy Master Plot, where we have specific time points for the finite time in terms of dissolution and absorption.

We also work now for the bioequivalence metrics and as well as the biowaiver.

Here are the articles we've published so far.

Here is the book published in 2023.

You can see here the schedule at the presentation for a AAPS webinar, and the presentation is a page meeting in Rome, Italy. Thank you for your attention.

Sam Raney: Our next speaker is Professor Hala Fadda from Butler University.

Hala Fadda (Butler University): Good day. This is Hala Fadda, and I'm excited to be discussing the challenges and opportunities facing the dissolution testing and biopharmaceutics classification of pediatric drugs and formulations.

FDA's BPCA and PREA have increased pediatric drug and biologics research and development, and as this chart shows, this has led to a substantial increase in the number of products with pediatric use information in the labeling.

However, these successes present us with new challenges. Despite the increase in approval of new drugs for pediatrics and new indications for already approved drugs, some of which the patents have expired or are about to expire, there's a lack of standardization with respect to the in vitro dissolution testing and bioequivalence testing of pediatric oral dosage forms.

Many USP mini dissolution apparatus have been developed. However, these have not been validated and do not reflect the dynamic nature of the gastrointestinal tract.

Further research is needed into developing in vitro dissolution tests that simulate pediatric gastrointestinal luminal volumes, composition and emptying rates.

Adult BCS is based on GI physiology and cannot be extrapolated to children. In adults, a drug is considered highly soluble when the maximum dose strength is soluble in 250 mL of aqueous media over the pH range of one to 6.8.

Now we know that it's difficult to give a glass of water to small children. And typically medicines are co-administered with juices or soft foods at much lower volumes.

In our lab we have set up a dynamic in vitro multi-compartment simulated stomach duodenum model SSD, and this integrates physiologically relevant fluid volumes, fluid transfer rates and pH of the upper GI tract of adult population.

Gastric secretions, gastric emptying rates, and emptying of drugs from the duodenum are taken into account.

The SSD model is physiologically relevant, and we have shown it to predict relative in vivo bioavailability trends of weakly basic drugs with solubility-limited dissolution.

Specifically, we have shown it to predict pH-dependent drug interactions, effects of fluid volume administration and prandial effects on trends in drug concentration profiles and effects of formulation changes on the supersaturation and precipitation behavior of weakly basic, poorly soluble drugs.

We have adapted the SSD model to pediatrics. Gastric secretion rate in children has been reported to be 2.7 milliliters per kilogram per hour, while the fasted gastric volume in children has been reported to be 0.4 milliliters per kilogram.

Therefore gastric volumes and secretion rates will vary with child age and need to be adapted, based on the pediatric population we are simulating.

And the means to extrapolate to the dosing volume used in the adult BCS. This can be ratio-based on the 40 milliliter gastric volume in adults and 250 milliliter dosing volume.

There is limited data on small intestinal fluid volumes in pediatrics. Mean total small intestinal fluid volumes were measured to be 30 plus or minus 24 in the fasted fed state.

However, large variability has been observed within the same age group and across different age groups.

Furthermore, the pediatric population medicines are frequently administered with juices and soft foods which have different physicochemical properties, specifically different pH, buffer capacity, osmolality and surface tension, and drug solubility can vary significantly between some of these vehicles.

It would therefore be important to develop different simulative media mimicking critical physicochemical properties that can be selected based on the class of drugs we are investigating.

The future directions are to validate the pediatric SSD model and to bridge in vitro drug release studies with PBPK modeling to predict in vivo drug absorption in pediatric sub-populations.

Thank you for your time.

Sam Raney: Thank you so much, Professor Fadda.

I'd like to welcome now our next speaker, Dr. Laura Phillips, from Spheryx, who will be providing an in-person presentation.

Laura Phillips (Spheryx): Thank you for the opportunity of speaking today in the area of meeting the challenges of establishing generic equivalency for biologics. I'd like to focus in on the area of safety and in particular, in the area of safety. I want to focus on the propensity of biologics to form protein aggregates.

And within the realm of protein aggregates, I'd like to focus even further into the small protein aggregate sizes of one to five microns. This is an area that, while it's thought to be particularly important in stimulating an immune response, it is understudied and under-monitored.

And the reason is that to date the technology that is broadly used in pharma are not up to the challenge of measuring protein aggregates in this size region.

What's needed in the technology is to have the sensitivity to reliably detect protein aggregates in this size range, the ability to differentiate protein aggregates from other kinds of contaminants that can exist in this size range, and the accuracy to provide reliable reproducible results for concentrations of particles in this size.

And, as I say, the technologies that are currently deployed broadly are not up to this challenge for this size range of less than five microns.

Those technologies now do exist. I want to explore with you the technology of total holographic characterization. I don't want to go into detail about the technology. But suffice it to say that the technology measures the holograms of particles, and from the holograms you get not just the size distribution in this size range of half a micron to 10 microns, but you also get the composition through the index of refraction. So it's an extra dimension of information. You can now determine what you have, as well as the size distribution of what you have of multiple particles, even when they're the same size.

Then you count the particles, divide by the volume and you get very accurate concentrations.

So let me show you some examples of how this technology has been put to use. These are some results that were published by AbbVie pharmaceuticals, using total holographic characterization and comparing it to flow imaging and resonant mass measurements, two techniques that are broadly used for protein aggregate detection.

There's four experiments here. All concentrations of the particles are the same. So these are all at about 5 times 10 to the 6 particles per milliliter, the Y axis. There is concentration. And note that it's a log scale. The first experiment is the control experiment all the way on the right is polystyrene, and you've got the measurements from the three different techniques. They all get the right answer. If you can't measure polystyrene, you should go home.

The next one next to polystyrene is a very easy to measure mAb, not typical, but these are three mAbs that AbbVie had these compounds. This first mAb is an easy to detect when it's not particularly translucent when it forms an aggregate, and you can see once again all three methodologies get the answer correct.

The interesting results come in the last two panels, where you see total holographic characterization is the only technique that continues to get the right answer. And the other two remember log scale here are off by orders of magnitude so grossly undercounting the amount of protein aggregates that are forming in this very dangerous and important size region.

Next is differentiation. Here you can see an IgG sample was put through a syringe, picking up different amounts of silicon oil from the syringe depending on the shear forces applied. If you look below you can see by size you can't distinguish whether you've got protein aggregates or silicon oil. Silicon oil is quite ubiquitous in the pharmaceutical industry in this size range.

But if you look at the refractive index, you can tell clearly what the composition is, and you can get accurate concentrations of both species simultaneously, so you can very easily focus in on the protein aggregates.

The last example here is looking at the degradation of polysorbate 80, which is the most common surfactant used in the pharmaceutical industry, and when it starts to degrade it forms oleic acid. We put that sample of degraded PS 80 through a syringe again picked up silicon oil, and you can see you can easily distinguish the oleic acid from the silicon oil.

When you have oleic acid in your sample. Here we have a sample of IgG that without any oleic acid, without any degradation of the PS 80, there are no protein aggregates present, but once you have the degraded polysorbate, you get lots of protein aggregation. So the technology here does exist. There's a wealth of information that is available, and it's an important region to monitor for equivalency and for safety.

Thank you.

Sam Raney: Thank you so much. Of course, generic drugs regulate a slightly different area than some of the content of your presentation. But putting that aside for a moment, are there applications in generic product development or assessment that you can see where research using these techniques might have value should be prioritized?

Panel Member: Yeah, certainly, in the area of peptide research, there could be an application for characterization of the aggregates.

I'm sort of curious, though. How does the composition, the composition part of the analysis work in terms of its specificity for the peptide over silicon oil, for example?

Laura Phillips: There are two characteristics that tell you what the composition is. One is the index of refraction. A hologram encodes all of the three-dimensional structural information about the particle. So you get the index of refraction, which is an inherent, objective, physical characteristic of the particle. And so that tells you very clearly if it's a protein aggregate or silicon oil or oleic acid, or whatever it may be. The second thing is that the symmetry of the hologram also gives you the morphology of the particle. The protein aggregates form with a very specific kind of morphology as they grow, so it makes it much easier to distinguish.

Sam Raney: Thank you. Thank you so much.

Our next speaker is Dr. Katherine Harris from Caroline Research.

Katherine Harris (Caroline Research): Thank you. I'm Katherine Harris, and I'm a principal research scientist at Caroline Research.

We work with life sciences, academic institutions, and other public and private sector organizations to conduct research on the delivery of healthcare and effectiveness of health care, using methodologies from economics, epidemiology, and patient-centered research methods.

Importantly, our company is a founding and continuing contributor to FDA Sentinel initiative, and I'm here today to speak to you about addressing a gap in the guidance around the assessment and generalizability of real-world evidence to clinically and regulatory relevant populations.

So earlier this year, Caroline research responded to an FDA solicitation for advanced research and the development of regulatory science. We proposed the development and testing of a conceptual and empirical framework that uses national health data to assess and enhance the representativeness of cancer screening rates derived from a large repository of health insurance information.

Our approach is highly relevant to FDA's interest in using real world data to generate evidence on the uptake and effectiveness of generic drugs in real world populations.

The representativeness of real world data is fundamental to the credible use of real world evidence to promote public health. The size, scope, and reliability of real world data has grown rapidly with the evolution of cloud computing, interoperability standards, the capabilities of data management systems as well as developments in the area of machine learning.

FDA guidance promotes the fit for purpose use of real-world data in ways that are transparent, reliable, and relevant. However, this guidance does not directly address representativeness as a feature of data quality.

Our proposed approach can help close this gap in guidance, using simple, well-established analytic approaches to assess representativeness of real world data and to enhance it when lacking.

We proposed work in four phases. The first is to calculate cancer screening rates for demographically and clinically defined subgroups using real world health insurance claims data and benchmarked data from CDC's behavioral risk factor surveillance system.

Next, we confirm the statistical reliability of the screening rates from both data sources using published suppression criteria. And then we quantitatively compare the two sets of rates using standardized mean differences. This is a widely used comparison strategy that helps us avoid misleading conclusions about comparability when comparing large groups.

Next, we use iterative proportional fitting known as raking to identify factors driving the lack of comparability between benchmarks and real world data. And finally, if needed, we use weights generated by the raking process to adjust the claims data to align with national benchmarks.

While promising, the application of this approach in the generic drug context requires highly integrated data from multiple sources with specialized features, including NDC codes to identify generic status of dispensed drugs, the ability to address bias due to confounding between utilization and disruptions in the supply of generic drugs and the ability to account for state regulations and other institutional requirements that affect the prescribing and dispensing of generic drugs.

And finally, the ability to account for undocumented utilization of generic drugs due to direct purchase.

The sentinel initiative and its many health plan and provider partners have the capabilities to integrate medical data on safety outcomes and pharmacy data documenting use of generic drugs across the United States.

Currently, however, the representativeness of these data is uncertain, and our approach can help facilitate assessment of the representativeness of fit for purpose real world data to promote the generalizability of real world data on generic drug safety, access and effectiveness.

Well, thank you. And in closing I appreciate the opportunity to talk about this different topic today.

Sam Raney: Thank you very much. So real world evidence is one of the areas in which we'll actually have several presentations, and those of our colleagues who are involved in evaluations of real world evidence, particularly as it relates to generic drugs. Do you have any questions or comments relating to some of the approaches and specifically, the proposal that Caroline research has brought forward? Is this research that resonates with you that FDA should be prioritizing?

So no comments at the moment. But thank you so much.

Our next speaker is Professor James Ferri from Virginia Commonwealth University.

James Ferri (Virginia Commonwealth University): Thank you very much for the opportunity to share a brief perspective and public comment regarding supply chain resiliency in pharmaceutical manufacturing enabled by seamless digital technologies.

So I'm from Virginia Commonwealth University, which has become somewhat of an epicenter in pharmaceutical process development, particularly in the API area. And so we're all familiar with the manufacturing sequence of events that moves from key starting materials through drug product.

And so when we think about this, this is really a system of systems that involves chemical transformations and their interactions with equipment and process analytical technologies to evaluate drug efficacy and safety. And so when we think about the provenance of a particular drug product, we have to consider both the regulatory starting materials from which it comes as well as the key starting materials from which we get that regulatory starting material.

And so this is a favorite graph of mine, which I call the chemical family tree. So 96% of all manufactured goods rely on this family tree which moves from at the top of the diagram from natural resources all the way through manufactured goods at the bottom, and so it turns out that the US is a net exporter of the light blue near the top there of chemical building blocks, and we're the first in the world as net exporters. But when we think about then what our pharmaceutical products, they typically live in the red area which are chemical intermediates, and the US is a net importer, second behind China in exports, a net importer of the red stuff. And so the universe of chemical intermediates relies on chemical transformations which have been largely exported to Asia Pacific during the last 15 years.

And so what we'd like to do is then just consider the case of a pharmaceutical, an API albuterol which is chronically in short supply. And so, when we first look at the registered route for producing albuterol from its regulatory starting material, salicylic acid. What you can see is that obviously there's a family of sequences. But that we can also understand from the use of AI and machine learning that there's a whole family of chemical possibilities of moving from different starting materials to that final target. And we are able to understand those things a priori before we use laboratory assets to validate or verify a chemical process.

And so then, using technology to first identify the route optionality, we can also simultaneously interrogate the provenance of the materials associated with those routes using trade data, both within the US and outside of the US. And so, as I pointed out, the US is a net exporter of regulatory starting material. So most of the things within the regulatory envelope from RSM to API are exported typically from Asia Pacific. And so I'm showing on the right there just what things are available from US imports, and what you realize is that nothing in the present process for albuterol, that is the registered process, is produced within the US. It's either imported from Asia, particularly China, or from India.

And so then that brings us to think about what options are available, then for domestic production. And so then, again, we can apply the same analysis to look at the regulatory starting material salicylic acid. And then we understand that we're moving further up that value tree and thinking about really those chemical building blocks. And when we look at, then route optionality again generated by AI methods of retrosynthetic analysis, we can see that there are abundant opportunities for manufacturing those materials domestically, which implies then that these supply chains could be reshored in the United States if there was a will.

And so, really, what I'm trying to point out is that we have an a priori capability of understanding what are the options and what are the range of options available to process development chemists for ensuring alternatives to drug shortages.

And so then, really, the retrosynthetic aspects of chemical manufacturing are only one part. Obviously, there's a significant engineering component. That's why we collectively term that chemistry, manufacturing and control section of the ANDA.

And so there has to be also technology that collects and understands the manufacturing requirements associated with those chemical transformations. And so here, what I'm showing you is just a snapshot of the chemical transformations associated with another drug atropine which is a very easy to make drug. There's only three synthetic steps yet there's more than 10,000 nodes and edges associated with the manufacturing requirements of a process to make atropine. So what I'm showing on the lower left is this is the sequence of manufacturing requirements associated with the equipment and the manufacturing requirements that go along together with the chemical requirements. And those things are typically decomposed, as I can show you in the upper left there across materials requirements and equipment requirements or transformation requirements with each synthetic step.

And so what we're able to do is then build a requirements model that both understands chemistry and the provenance of materials and equipment. And then look at the availability of that equipment in databases that curate the assets associated with chemical manufacturing, and so what I'm showing you here is a concept that we put forward in a white paper, and later in a response to a BAA, to the FDA.

To understand, for generic drugs, particularly generic drugs in short supply that we can curate all of the options associated with each drug target, and scores associated with their starting materials prominence, their manufacturability, scores like ESG or the cost of manufacturing associated with both the raw materials and the manufacturing costs.

And we could understand the risk intrinsically associated with the present route, as well as comparing that present route to the family of options that are available as alternatives. And so what we've begun to do is curate national registries of manufacturing assets. So I'm just showing you below a map that does some cGMP manufacturing asset registry for North America, that we can understand where these alternatives can be executed both in United States and abroad.

And so again, if we want to consider portfolio level decisioning across drugs that are in short supply, we need digital technologies to both address retrosynthetic options as well as equipment and manufacturing options, which would be important for informing strategic policy decisions from organizations like the FDA or the Department of Defense, as well as when we consider sourcing and procurement initiatives associated with industry.

And so with that I will conclude and thank you for your attention and welcome discussion.

Sam Raney: Thank you. Fascinating talk. So maybe I'll begin with our industry colleagues: are supply issues for APIs for generic products a challenge area that we need some research in?

Panel Member: I'm curious to know. What's your data source? And you mentioned AI has been used. Can you elaborate a little bit more on how you apply the AI to support the work?

James Ferri: So this is a combination data science problem and AI. So when you consider retrosynthetic alternatives, we use AI technologies to understand what are the synthetic options, and that AI is trained on the family of chemical literature that either is academic or from the intellectual property databases that are available. And so those are available in machine readable form.

And so we make inference from those machine readable forms of what synthetic possibilities exist. And then those can be validated against existing literature that is adjacent to those reactions.

Panel Member: So it's more like an information retrieval kind of function based on the AI?

James Ferri: Well, it's actually a machine learning regression. So for example, when you think about synthetic chemistry, we think about it in terms of functional groups rather than molecule identities. So if we knew the identity of all molecules that have ever been transformed, that would still only represent a subset of what could be done. Because if you think about an organic chemistry, an R group represents a collection of other possibilities. So a methyl group could be an R group. An ethyl group could be an R group. So, understanding the chemistry of what happens in the presence of an R group is different than understanding what happens when that R group is an ethyl.

Panel Member: I have a quick question. So there are so many different starting materials. So at least at this stage, are you trying to work on all the approved drugs or you have more broader goals?

James Ferri: So when we think about scoring and as you mentioned, the combinatorics get explosive. So there's really a large number of possibilities. But when you impose other criteria like price or provenance or supply security, then the retrosynthetic options become more narrow and addressable, but there still are a large number of options. So, but we go from tens of thousands to hundreds, or even tens of options. So by considering simultaneous constraint problems, we get to a much more narrow collection.

Sam Raney: Thank you very much. So it's an excellent presentation.

Next set of presentations will be virtual presenters. First one will be from Kathleen Walsh from Boston Children's Hospital

Kathleen Walsh (Boston Children's Hospital): Hi, I'm Kathleen Walsh. I'm the director of the Patient Safety Research program at Boston Children's Hospital, and I'm excited to speak to you today about measuring the safe use of generic pediatric medications at home.

I'd like to start with a clinical case from my research. An eight-year-old child with type one diabetes, depression and ADHD takes insulin, methylphenidate, sertraline, and as needed glucagon and acetaminophen.

After school, if her mother is working, her twelve-year-old sibling helps her check carbohydrates, adjust her insulin dose and administer her insulin.

During our research home visit, her mother dialed the correct insulin dose on the pen after adjusting for carbohydrates, however, she pulled the pen out immediately after administering the dose, causing the insulin to squirt out for the child. You can see the photos.

This is a good example of some of the problems or challenges with home medication use in children, including having multiple caregivers. Also, there are times that children need to take liquid medications or cut and crushed pills and the doses are based on weight. So they vary.

I've spent 25 years working with families to understand safe use at home, including use of drug device combinations in the treatment of asthma in stopping seizures or in the treatment of type one diabetes or other conditions.

The methods I developed are shown in the next slide.

In the hospital, observation is used to understand nurse administration errors. So I developed analogous methods by placing a trained researcher in the home to observe parent administration.

We also perform a medication review and interview parents, and we perform a chart review after leaving the home.

These methods go beyond task analysis or human factor studies into the real world of the home environment where multiple medications are administered by multiple caregivers.

Let me show you what we found using these methods.

In these several studies we have performed a total of 545 home visits where we have found that errors are common and dangerous. For example, in one study 10% of children with cancer were injured by an outpatient medication error over a 6 month observation period.

This is a similar rate to the rate of injuries by medications in hospitalized patients.

Oral medication errors were the most frequent cause of injury in every study and drug device combinations are especially challenging.

What is needed to improve the safety of medication use at home?

The good news is that errors at home can be prevented by interventions in the clinic or pharmacy, such as the many references I've shown below.

But the bad news, according to an IHI report, called "No Place Like Home: Advancing the Safety of Care at Home" is that widespread use of these interventions is limited by a lack of measures to evaluate the impact at scale.

In order to begin to address this gap, funded by the FDA, we performed a scoping review of the literature, including published and gray literature where we found no scalable measures of medication administration errors. There were a few measures that were really research grade and not scalable, very complex.

In FDA funded interviews and concept mapping with key partners, including parents, pharmacists, and organizational leaders, we found these—we generated these different types of measures that were proposed by these groups.

And in quantitative surveys, the groups prioritized measures of safe administration at home as the top priority for development.

Informed by this preliminary research and building on 25 years of experience, we propose to develop scalable measures of safe administration at home by developing measures and testing the reliability and validity of survey measures, scalable survey measures of safe use at home, and then assessing the association between these reliable, valid, scalable survey measures with medication errors and harm, using our existing home visit methods.

Such scalable measures would be immediately available to health systems, pharmacists, and others seeking to improve the safe outpatient use in children.

Our team includes pharmacists and physician leaders who are well positioned to implement these proposed measures nationally, and this proposal is well aligned with the FDA's vision to eliminate medication errors in the US healthcare system. Thank you.

Sam Raney: Thank you. Our next speaker will be from Dr. Alexa Simon Meara from Ohio State University.

Alexa Simon Meara (Ohio State University): Hi, my name is Alexis Mierra, and I'm a rheumatologist in the division of oncology at the Ohio State University, and I take care of immune-related adverse events by the complications of immunotherapy. And what I want to talk about today is topic 8 for the FDA: real world evidence.

I have three slides. So hopefully, they will go pretty quickly. Fundamentally, we're going to talk about real world evidence and some of the barriers and obstructions I see, and my hope is that the FDA can stir some discussion about how we can best make some solutions regarding this.

Real world evidence is dependent on claims data, and often ICD 9 and 10 codes, or how we bill. How we bill, or how we code, is often relevant to how we get access to drugs from insurance companies and PBMs. However, due to the situation of insurance companies and PBMs, we've had a significant issue of actually getting access and patients drugs that are needed due to evidence algorithms, stepwise therapy, and so often physicians will kind of work around or add various other codes that need to be done to be able to get access to drugs for patients.

So therefore, that makes the reliability of claims data very unreliable. And then, if we're going to buy data and do these big claim databases, you still need a chart review, and then, therefore, our claims data is always going to be flawed, because that material that we need to really understand what the disease is or the treatment, we won't have access to the notes.

Two, on that same point of real world evidence and AI algorithms. If we're going to use natural language processing and different things to extract data from the notes so we don't have to do lengthy chart reviews that are incredibly expensive, we have to have large validation cohorts. This is just like biomarkers, right? The more people we tested on, the more ways we can see algorithms. And therefore, how do we ensure we have a diverse population? What is the power required? How do we have enough patients to be able to look at algorithms? And particularly in disease states that are more complicated, like heart failure or rheumatoid arthritis, that may not

be a one and done, or hypothyroid that just one test one or the other. So how do we best look at that? And how many do we need? And who should be paying for that? What is the evidence we need and who's going to help structure this so this could be done correctly, because we can all make algorithms that if you wear purple on Tuesday that maybe you're more risk for something. But how is that clinically relevant?

And lastly, how do we talk about large populations? So we just talked about you need bigger cohorts. You need diverse cohorts. How do we deal with ICD 9, and not chart reviews. But how do we do this in the silos of academic medicine, when data sharing has become more and more difficult. And if you're going to buy databases again, it's only claim-based that doesn't have access to the notes. So fundamentally, we are handcuffing ourselves in the sense that we're not combining data together. We are not a socialist medicine country, like some of the European countries, where they can look at data and follow patients over time.

So how do we do this with the constraints that we have in the United States? Who should provide these data? How should we bureaucratically legally—is this something the FDA should be doing, and how we best do this, and how we house data and how we then look and request data to do trials and to do safety of drugs.

These are the questions and the conversations I wish we could have in a larger scale to actually impact academic medicine. So we can make more important statements about real world evidence that actually is impactful, how we can drive hypothesis and have better drug use and safety of drugs and maybe more precision medicine of what drugs work for what population in those settings? Thank you for your time. And I look forward to this further discussion.

Sam Raney: Our next presenter is from Professor Jacqueline Griffin from Northeastern University.

Jacqueline Griffin (Northeastern University): Good afternoon. My name is Jacqueline Griffin. I'm an associate professor of Industrial engineering at Northeastern University. I appreciate the opportunity to come here today and present my thoughts on proposed research areas at this public workshop.

To begin with, I wanted to first identify where my research and my expertise aligns with the priority initiatives that were publicly distributed.

Looking here, we find that we highlight improving the use of real world evidence for post-market surveillance of generic drug substitution for evaluating the impact of generic drugs on public health.

At the core of this focus is using data, using new analytical methods to try to really understand the role of generic products within the marketplace.

Correspondingly, my research over the past 10 years has really focused on understanding and modeling the broader dynamics of pharmaceutical supply chains and really understanding the effects of disruptions or shortages within the system more broadly.

So we know that the critical role of generic drugs is to increase patient access to medication while also reducing patient costs.

And if we think about it, while there's many aspects that come into play in meeting this need, one of these is addressing the role that generic products play with respect to drug shortages.

So the surveillance of generics with this focus on drug shortages really could mean many different things. For example, it could mean detecting which generic products have the greatest public health impact if, in fact, there was found to be poor quality or manufacturing issues, or the need for production suspension or a product recall.

It also can highlight the role of generic products that are currently being used to alleviate drug shortages or to mitigate those effects.

And as many in the room are aware, generic products are one of the largest classes of products that are among the drug shortages every year.

So let me give you a bit of background about my research team at Northeastern. For close to a decade we have been focusing on looking at the interactions and the system dynamics related to the role of the information that is available within the pharmaceutical supply chain. How that information about drug recalls affects decision making everywhere from the hospital all the way up to the manufacturer. Correspondingly, we want to understand how different decision making in the wake of these shortages, also, the different system designs or system complexities really drive what we see in the broader behavior of drug shortages.

So with a focus on proposed research focus, I've highlighted three here that I think is relevant related to this group.

First, we can think about identifying those generic products that are too big to fail, and for which quality or production issues would, in fact, drive those significant market shortages. And in turn, the reason for this was that it would really inform prioritizing surveillance based on public disruptions or quality issues or impacts of production disruptions.

It, giving us a key to say, well, where should we be looking first if we really want to ensure that we're thinking about public impact pertaining to shortages. This can also include identifying trends that we see in shortages. This could be spatial temporal trends that we see in terms of how do shortages evolve? How do generic products come in to resolve those or mitigate those effects?

What are the general patterns or early methods of detection we can see for products that potentially could have a shortage in the future.

Also, we can think about identifying what information is needed. What is the information infrastructure needed for answering these questions from the future which could then inform designing that new infrastructure?

I appreciate the opportunity to talk to you today. I provided my email address here in case anyone would like to contact me or ask any questions about what's currently going on, or to discuss opportunities or new research ideas.

Sam Raney: Thank you so much. Our next presenter is from Dr. Molly Moore Jeffrey from the Mayo Clinic.

Molly Moore Jeffrey (Mayo Clinic): Thank you so much for the opportunity to provide some comments today. My name is Molly Jeffrey. I'm a researcher at Mayo Clinic and co-PI, with Joe Ross at Yale, of the Yale Mayo clinic center of excellence in regulatory science and innovation or CERSI.

In our work with the FDA we help conduct research that addresses important gaps in knowledge in regulatory science, and we help to develop research methods and approaches that support the mission of the FDA and support regulatory decision making.

One of our key areas of expertise is the use of routinely collected real world data sources like insurance claims and electronic health record data, we use that to inform regulatory decision making.

So while randomized controlled trials will always be an essential approach to understanding drug efficacy, thoughtfully conducted studies using real-world data can provide evidence that you can't realistically generate from an RCT. So some examples of studies completed by our CERSI team illustrate some of the strengths of real-world evidence in practice.

Dr. JP Brito and team assessed generic to generic switching of thyroid hormones. Levothyroxine is one of the most commonly prescribed drugs in the US. There are a bunch of generics available. But uptake of those generics has been lower than would be expected, and one of the reasons could be a concern about substitutability of the different preparations which was actually raised in a 2014 American Thyroid Association guideline. So the team was able to use a large data set, OptumLabs data warehouse of linked insurance claims and laboratory data to demonstrate there was no difference in TSH levels among patients who switched among generics compared to people who did not switch.

The cohort included almost 16,000 people from across the country. We completed this, obviously, for a small fraction of the cost and the time that would be needed to conduct a similar prospective study.

In another of our studies, Dr. Rozalina McCoy and team used the target trial emulation framework to emulate a really important RCT that looked at therapies added onto metformin for people with moderately uncontrolled type 2 diabetes, the GRADE trial.

The emulated trial that we did identified similar effect estimates as the big RCT. But in a cohort that was more representative of the overall population with diabetes, and the emulated trial was actually completed and published before the RCT. So this was a really important test case for methods where researchers could not have been guided in their approach by knowing the RCT results in advance because the RCT had not been published.

A third study was one that I led, looking at prescribing patterns of opioids only labeled for use in people who are opioid tolerant when they start the drug.

Previous studies had used claims data, had looked at this issue and found that a large proportion of patients starting the drugs did not appear to be tolerant when they started.

But those studies only using claims data, people had some concerns that they might be missing something from opioid prescriptions. So we used linked EHR and claims data to see if we could find any additional evidence of tolerance when we looked in the text of clinical notes, and when we looked at prescribing information in the health records.

Using this more comprehensive data source, we found minimal additional evidence of opioid tolerance and continued high rates of potentially unsafe use of these drugs and presented that to the FDA.

We would encourage further exploration of real-world data studies which we really think can directly address the research priority areas around comparisons between generics and reference drugs or among generics in postmarket surveillance and a few ideas we've been thinking about are here. So as a follow-on to the work on levothyroxine, we've been thinking about whether there are other drugs where brand use is persistently high, and where we could look for potential signals of concerns about effectiveness, equivalence, or, in the case of drug device combos, even usability, including signals, like different rates of switching drugs within a class, different rates in persistence of use and differences in dose escalation patterns.

A methodological question in authorization of generic is whether people expect to do worse when they're switched to a generic which can obviously impact their outcomes. We're curious whether we could use cases where there are both authorized generics and other generics available to assess this potential nocebo effect, and the results could be used then to inform future work where there's no authorized generic of what that effect might be. And then, finally, we also think the target trial emulation framework could be a useful approach to comparing brand and generic drugs and particularly in cases where there may be signals of a bioequivalence issue. So I hope these comments have been helpful, as you consider generic drug research priorities, and thank you again for the opportunity to provide our thoughts.

Sam Raney: Thank you so much. Our next speakers are from Drs. Ozlem Ergun and Daniel Kosmas from Northeastern University.

Daniel Kosmas and Ozlem Ergun (Northeastern University): Hello! My name is Daniel Kosmas, and today I'll be presenting on research opportunities for mitigating drug shortages through better inspection planning.

As I'm sure some of you are keenly aware, drug shortages have been a persistent problem in American health care for over a decade now.

Between 2011 and 2020, there were over 680 active drug shortages reported, and in recent years the number of drug shortages has been climbing.

Even in the first quarter of this year there was a record high number of 323 active shortages.

And these shortages have had numerous public health impacts, including patients receiving less effective treatments or potentially having their treatments delayed or cancelled, which results in negative health consequences.

In 2019 the FDA reported that 62% of drug shortages were associated with manufacturing or product quality problems, whether that be due to substandard manufacturing processes or quality defects in the finished products.

Academic literature has found that more frequent inspections can act as an inhibitor to quality decay which can in turn result in less unexpected disruptions.

However, this is a narrow view of the problem as a whole.

On the one hand, more frequent inspections will be more resource intensive to the FDA.

On the other hand, pharmaceutical manufacturing companies may be required to perform more maintenance than is actually optimal.

And in the case that this results in a significant loss in production can result in supply shortages as an attempt at preventing the issue.

Additionally with more maintenance is more maintenance costs which may make a product lower profit.

This lower profit could make it more beneficial for the manufacturer to discontinue the product as opposed to performing the maintenance which can cause a longer term supply shortage.

Given the complexity of this topic, the problem now becomes: how can the FDA ensure compliance with regulations while also ensuring that production is profitable for the manufacturers so that way these companies are not unintentionally forced out of the market.

There are numerous opportunities for research on these topics.

One example is, how can the FDA better utilize AI and ML techniques to determine how frequently facilities should be inspected and given a limited budget which facilities should be prioritized.

Additionally, can data sharing between the manufacturers and the FDA result in reduced costs both for the FDA and for manufacturers.

Given all of these techniques and data sharing, can the FDA get a better sense of issues in the larger supply chains of substitutable products which may allow them to make their inspection decisions in a way that can better mitigate drug shortages.

We believe that research addressing inspection policy will be the key to helping mitigate drug shortages.

Thank you so much for your time and attention.

Sam Raney: Thank you. Our next presenter is Dr. Fang Yu from Continuous Pharmaceutical Inc.

Fang Yu (Continuous Pharmaceutical Inc.): Hi, I am Fang Yu from Continuous Pharmaceutical Inc. Today I will talk about the AI and machine learning application for ANDA submission.

There are challenges and motivations. AI and machine learning can be used for checking compliance of ANDA submission and summarizing real-world evidence for generic drug adverse events.

To assess the compliance of the ANDA submission, the document from the ANDA submission and the prompt from users were served as input.

Some tools, such as ChemSketch or ChemDraw, can be used to convert chemical structure to IUPAC name within the document and to develop AI assistant.

The few-shot approach can generally use the historical ANDA data, ANDA document to get example input and output. And then those examples can be used in the prompt to instruct large language model to perform the similar task for the new ANDA submission.

For example, with the using of the AI assistant, they can summarize the document or the report, checking the compliance of the ANDA submission by comparing with the regulatory requirements, doing initial regulatory assessment for the consistent error for meeting or the graph, and finally predicting potential issue or risk for ANDA applicants in addressing issue earlier or speeding up the FDA decision making.

Machine learning classifier can be used to summarize the real-world evidence of the generic drug adverse events.

The inputs will be textual documents. Classifier model can efficiently classify with a large volume of the documents into different pre-defined labels for the data analysis and integrations as well as for signal detection of the adverse events.

Machine learning classifier can speed up signal detection and classification of evidence.

So with the AI classifier model, a vast amount of the diverse data, such as electronic health records, prescription records, adverse event reports, product reviews or the consumer complaints, phone call and video can be summarized and classified into the different pre-defined labels.

The model classifier also can be used to detect potential adverse events or monitor real world evidence.

To summarize, AI and machine learning can speed up checking compliance of the ANDA submission and efficiently classify and detect adverse events related to the generic drug usage.

Thank you.

Sam Raney: Thank and our next speaker is Professor Dongmei Li from the University of Rochester.

Dongmei Li (University of Rochester): Hello, everyone! My name is Dongmei Li. I'm currently Professor of Clinical and Translational Research, Obesity and Public Health at the University of Rochester. I want to thank FDA to provide me this opportunity to make some comments on the FDA public workshop.

My comment focuses on the predictive tools for generic product development and assessment.

Specifically, I want to comment on expanding the use of artificial intelligence and machine learning tools to improve the use of real-world evidence for post-market surveillance of generic drug substitution for evaluating the impact of generic drugs on public health.

The current post-market surveillance program is limited, considering the increasing number of manufacturing facilities.

Real-world data in the post-marketing surveillance period has potential to overcome this limitation. I want to talk about two case studies.

The first case study using the FDA sentinel initiative, distributed data network, identifying clear differences between manufactured products and the second case study comparing the brand and two generic versions of a specific drug which leads to recall.

Sam Raney: We appear to have lost audio for the online attendees. So we're just pausing for a moment to resolve that.

Dongmei Li: Or the generic versions during the initial generic marketing period due to their increased adverse events.

But how do we use AI and machine learning tools to help us with the challenges.

So I want to talk about several points. So first, AI tools, such as the natural language processing tools, can be used to analyze electronic health record data, social media data and also online forums to identify potential adverse events and concerns about generic drug substitutions.

Also, machine learning algorithm can be used for early detection of potential issues of generic drug substitutions by analyzing large real world data. For example, the claims data.

We could also use AI algorithm to build predictive models for potential outcomes of the generic drug substitutions using historical and real world real-time surveillance data.

And also, we can use AI system to build the real-time alerts and notifications to provide to the FDA, patients and healthcare professionals in terms of the potential issues of generic drug substitutions.

And also with AI/ML algorithm, we can realize personalized medicine with tailored treatment for each patient based on their unique characteristic. Therefore, we can improve the efficacy and also the safety of generic drug substitutions.

And the impact of the generic drugs on public health could also be evaluated using AI tools to identify specific patterns and trends for regulatory purpose.

Also, we can use AI tools to examine the compliance with regulations and guidelines related to generic drug substitutions to monitor them.

AI tools could also be used to assess the drug efficacy by analyzing clinical trials and also real-world evidence of the generic drugs and their brand counterparts to see the difference.

AI tools like natural language processing algorithm can be used to summarize and analyze large volume of literature, especially on the safety, efficacy and utilization of generic drug substitutions. Therefore, this result can inform FDA for the decision making.

So finally, this is a reference I used for the comment. Thank you so much for your attention.

Sam Raney: Thank and our next presenter is James Hasty from BHEC.

James Hasty (BHEC): Hello, everyone. My name is James Hasty, and I'm the CEO and founder of BHEC Incorporated. I'm here to talk about enhancing the ANDA process with AI and ML for prescription drug efficiency.

A little background. The abbreviated new drug application or ANDA process is critical for the generic drug approvals and challenges, increasing workloads, manual reviews, risk evaluation of mitigation strategy requirements or REMS requirements and resource constraints.

The solution: artificial intelligence machine learning AI/ML tools, revolutionized the ANDA process and reduce the challenges. Pain points of the ANDA process.

Benefits of AI/ML tools. One speed and efficiency. AI algorithms can analyze vast datasets faster and with better accuracy than humans. It can even accelerate the ANDA reviews, reducing approval times while maintaining integrity and objectives of those reviews. It can automate routine tasks, provide risk assessment based on drug formulations and manufacturing processes, automate regulatory reports and documentation. It can even monitor adverse events reported after drugs approval to identify potential safety concerns with the product.

Three quality assurance. AI/ML can detect anomalies ensuring data accuracy, even improve consistency and reliability and regulatory decision making.

What is the impact of AI/ML also for predictive modeling? One, it can predict bioequivalence outcomes. AI can predict bioequivalence outcomes based on formulation data. It can also perform virtual bioequivalence, utilizing modeling and simulations in lieu of clinical sites.

It can identify potential issues early based on historical data, product recalls and regulatory enforcement actions which can assist with the review process.

We can develop AI/ML models to assess the risks associated with specific drug formulations, manufacturing processes or regulatory strategies.

We can employ techniques like ensemble learning or deep learning to integrate information from multiple data sources and improve the risk assessment accuracy. We can employ techniques like logistic regression, random forest or deep learning for adverse events and predictions.

What would the future of AI/ML tool usage within the FDA look like?

One personalized medicine. AI/ML models will play a crucial role in advancing personalized medicine approaches within the ANDA process by analyzing patient data, genetic information and clinical outcomes. AI can help identify patient subpopulations that may benefit from specific drug formulations or treatment strategies.

Two regulatory compliance automation. AI tools will be used to automate regulatory compliance tasks within the ANDA process, including document preparation, submission tracking and compliance monitoring. Natural language processing algorithms may be employed to analyze regulatory guidelines and streamline the submission process.

Integration with emerging technologies. AI/ML tools will be integrated with emerging technologies such as blockchain and many other things and augmented reality to create innovative solutions for drug development and regulatory compliance.

For example, blockchain technology may be used to ensure the integrity and traceability of clinical trial data, while IoT devices may enable real-time monitoring for drug manufacturing processes.

And finally, real time monitoring and surveillance. AI/ML algorithms will be used for real time monitoring and surveillance of drug safety and efficacy within the postmarket phase, automated adverse events detection system, pharmacovigilance algorithms and social media monitoring tools may be employed to identify emergency signals and monitor drug performance in real time.

In conclusion, the implementation of AI and ML within the Food and Drug Administration's abbreviated new drug application program is imperative for several reasons.

One AI/ML can significantly enhance the efficiency and accuracy of the regulatory review process by automating routine tasks such as document parsing, data extraction and regulatory compliance modeling.

Two AI models can provide predictive insight into drug formulation optimization, regulatory compliance prediction, risk assessment, and adverse event monitoring thereby improving decision making and accelerating the approval process for generic drugs.

Three. The integration of AI/ML technologies can facilitate real-time monitoring and surveillance of drug safety and efficacy during the postmarket phase, ensuring timely identification of emergency signals and enhancing patient care.

And finally, by leveraging AI/ML tools within the ANDA program, the FDA can streamline operations, improve regulatory oversight, and advance public health outcomes in a rapidly evolving pharmaceutical landscape.

I'd like to thank everyone for your time today. Again, my name is James Hasty, and I am the CEO and founder of BHEC Incorporated where we augment expertise with technology.

I can be reached at j_hasty@audittech.net again, Thank you for your time.

Sam Raney: Thank Mr. Hasty and our final public presenter before the break is Peter Gomper from Rubitel.

Peter Gomper (Rubitel): Good afternoon, and thank you for the opportunity to present a proposal for future research.

It is well understood that protecting a drug, including many generic drugs from environmental degradation is crucial for maintaining the effectiveness and safety.

A key issue in generic drug development and approval is proving bioequivalence. However, like their brand name counterparts, some are vulnerable to environmental conditions, particularly temperature fluctuations which can drastically change their chemical structure and degrade active ingredients.

Unfortunately, unit-level monitoring as a data log for time, temperature, UV radiation and humidity in real-world environments is rare or non-existent, challenging the accurate determination of cause for an adverse effect.

In support of data comparability for bioequivalence and pharmacovigilance studies, we propose the FDA support research in this area.

Insightful findings and potential advantages include maintaining drugs intended potency and effectiveness throughout its shelf life, detecting the frequency of adverse effects from degraded substances, reducing the need to discard drugs due to spoilage, lowering healthcare costs for both patients and providers, generating real-world data on drug's ability to support refinement of generic formulations and enhance stability relative to real-world conditions, promoting generic acceptance by healthcare providers and patients by building confidence in generic drug efficacy and safety.

Unit-level digital monitoring also enables one with the opportunity to integrate real-world data and clinical data valuable source. To conclude digital diaries which allow patients to record medication usage and side effects in real time, surveys which capture patient reported outcomes, combined device and apps designed, for instance, to continuously track health metrics like heart rate or activity levels as well as patient-approved access to clinical electronic health records.

By combining drug stability monitoring with real-world data, the opportunity arises to enhance the application of artificial intelligence and machine learning for generic drug development and approval.

AI/ML can be used to predict drug degradation patterns and shelf life from real world data encompassing a much broader spectrum of information derived from very diverse patient populations across various environmental settings, reflecting the multifaceted nature of health experiences and outcomes.

Analyses promised to support patient information leaflet updates regarding storage conditions and other important information, such as interaction with other drugs, effects of patient behavior, such as driving or operating machinery and information on special populations.

Combined, adverse drug reactions and environmental exposures data sets can be efficiently analyzed for pattern analysis to quickly identify trends not previously identified during bioequivalence studies.

Analyzed data can be used to guide the development of robust formulations less prone to environmental stressors or patient behaviors, improving drug safety and effectiveness.

Integrating therapeutic effectiveness with environmental monitoring enables AI models to tailor treatment plans based on individual responses.

The synergy between stability monitoring, real-world data and advanced analytics, promises to significantly enhance drug development, safety monitoring and personalized healthcare delivery.

Again, thanks very much for allowing me the time to present this research topic. I look forward to receiving your questions.

Sam Raney: Thank you, Mr. Gomper.

And so that concludes our marathon session of 30 public comment presentations. What I came away with was seven areas in which research was being recommended to be prioritized. One was the characterization of complex APIs and their impurities. Another was the characterization of immunogenicity, the approaches and the standards. Also methods to be developed for bio-relevant in vitro release for long-acting injectable products. Also drug device combination products and understanding a little bit more about the focus and context of their use, and the users. More about integrated in vitro and in silico approaches to characterize the arrangement of matter and to predict product performance. Also, in the oral products area, focusing more on bio-predictive dissolution, looking at fed and fasted effects and physiological implications for how that may change bioavailability under each. Also, when it comes to looking and understanding the physiological conditions, how that might extrapolate to pediatric conditions. Looking at areas to look at real world evidence, and post market surveillance for generic drugs and other areas as well. And what I'd like to do is as we head into the break, I'd like to give you an opportunity to collate your thoughts and your notes.

As soon as we come back from the break we'll be having our two faculty presentations. They will be giving us some perspective about conversations, numerous interactions they have had, and that they're able to synthesize the feedback from industry about what are the most pressing challenges for generic product development. So we'll hear about that. And then, as we move into the panel discussion, I'd like to begin by going down the row through all of our panelists and collecting what really stood out for you. And so this, perhaps something that you can do even during the break is, look at your notes and kind of identify what really stood out for you as those research areas that really need to be prioritized as we move forward, and with that I'll say we can break a couple of minutes early for our 11:15 break. But I would ask in return that everyone is here promptly for 11:30. We will be starting on the dot at 1130 with the professor, Anna Schwenderman, and just out of respect for everyone being here when she begins her talk, I'd invite you to get some coffee, have your bio breaks, stretch your legs, and please be back here at like exactly 1130. Thank you.

Session 3: Public Comments - Part 2

Sam Raney: Welcome back. It is 11:30, and I thank you all for coming back. I welcome Professor Anna Schwendeman to give our next presentation. She and Dr. Prabhakar Reddy will be giving us insight from the CRCG and US Pharmacopeia.

Both are illustrious individuals. I invite you to go to the website for the full biographies, and for that matter, the full biographies of all our distinguished individuals on this panel. With that, I'll say Dr. Anna Schwendeman will be providing industry interview feedback focusing on the main challenges in the development of complex generics. Professor Schwendeman.

Anna Schwendeman (CRCG and Univ. of Michigan): Well, thank you so very much, Sam, for the kind introduction and for having me here to present. The only reason I'm here is because in 2020 there was a call for applications to start the Center for Research on Complex Generics, which was in a way a brainchild of Rob Lionberger and Jim Polli. I applied for this grant, and we got it during COVID. Then we started a lot of activities during COVID. I think I gave this presentation twice virtually to large audiences. This is the first time I'm giving it in person, so I'm very much looking forward to it.

The center is between the University of Maryland and the University of Michigan, with very good collaboration with the United States Office of Generic Drugs of the FDA.

Our mission in the center—as everybody here in the audience, we all have the same mission—is to increase access to safe and effective generic drugs. We have three main arms: enhance infrastructure and communication, improve education and workshops, and have research collaboration across industry, academia, and FDA.

We all are working in this area. Perhaps the only difference that we bring is from the beginning of the start of the center, we decided to be very inclusive and try to listen to all sides. The problem statement came from Rob Lionberger. He said we see generic industry in biennial meetings, and nobody really tells us exactly where the issues are. So we said okay, and then we also would like to tell back and describe what are our issues with the review and how we see the field. From this perspective, we always try to be, as Andrew Babinski calls us, honest brokers. This is the only difference in our approach.

Here are our three main arms. One is infrastructure and communication, so we routinely interview generic companies, stakeholders, and various organizations. I'm presenting today the outcome of those interviews. We also provide education and training workshops. Then we have some collaborative research projects. This is the area that I really would like to enhance if we receive this grant for the next five years, because I think we have a way of collaborating between both FDA and industry on joint projects. If you think it's impossible, look at nitrosamines. This is the area where generic industry and innovators collaborated in such a nice fashion, as we saw yesterday in the presentations. We would like to focus our collaborative research as well on a couple of specific projects if possible.

Workshops and Activities

From the start of the center, we held 14 educational workshops and training sessions in total. We have over 27,000 participants registered. Since last year, we started to have in-person components. You can see it's a lot of fun. Here are some pictures of our in-person workshops. Usually we have about 100, less than 100 attendees in person, but we also have nearly 1,000 attendees virtually present at those workshops, depending on the topic. I highly encourage you to make a point to show up in person. This is a wonderful place where the agency listens to your feedback, and you can ask directly some of your questions and phrase your concerns. It's only by talking together that we can improve and achieve our goal. Remember, we all have the same goal in mind.

There are three workshops remaining for this year. The first one is the popular topic of this morning: immunogenicity of generic peptides and oligonucleotide drugs. The next one, another popular topic from yesterday, is nitrosamines—the second workshop on nitrosamines we are conducting. Finally, in December, we are doing a workshop on low global warming potential propellants transition.

We have some research projects, some small research projects. We also have some research projects that we outsource that are not listed here. I really hope we could do more collaborative projects with the industry. The good part about research projects is we have a wonderful website where you can track all the outcomes of the entire GDUFA research priorities. Toward the end of my presentation, I'll point you to how to do it.

Industry Interview Findings

This is the core of my presentation. These are our ongoing engagements with generic industry. We had over 750 various interviews. We interview major generic companies, smaller specialty generics, and various stakeholders like USP, AAM, and others. We are grateful for all of you who agree to be interviewed by us, and whoever has not done it, please let us know. We would like to continue those interactions. Only by having good data will we get our best information.

Here's how we perform those interviews. First of all, we establish relationships, and in many cases we have CDAs. Sometimes we meet in the presence of the agency and industry, sometimes just the CRCG. We have periodic meetings. We try to do this about once every year between this variability, and then we try to summarize the outcome in presentations like this and also publications.

Here are the general outcomes of all of our interviews. The first four really mirror the four sessions that we designed for this workshop. Number one, by the number of feedback, was characterization of complex generics: complex formulations, complex excipients, complex analytical methods, and also complex APIs and immunogenicity of peptides, oligonucleotides.

Number two was nitrosamines.

Number three was drug-device combinations and human factor studies.

Number four is clinical trial design and alternative approaches to endpoint studies, especially when they apply to specific populations: pediatrics, orphan diseases, but also long-acting injectables and antipsychotics or inhalation products.

The next two are more—not science-based, but intellectual property guidelines and communication. Those are not science topics, but they're highly influenced by the science, and they many times prevent approval of medications. This is the area of big discussion between the industry and the agency.

Specific Challenges

Complex Generics Characterization
Industry comment: "Industry knows how to validate HPLC methods very well, but we are now expecting all those complex methods, and there is no way we expect them to validate the same way. We cannot know exactly what the methods are."

Really, if you look at those three topics: one is complex products and complex raw materials; the second one is complex analytical methods, particle size analysis, in vitro relevance dissolution; and then number three is complex APIs—peptides and oligonucleotides. How do you analyze them? The basic mathematics is that if you cannot synthesize all of those impurities, you will have thousands and thousands of them for oligonucleotide products.

Take COVID-19 vaccines. Most of us got this product. It's a very complex product. Not only is it an oligo product with all the potential impurities, but it's also a lipid nanoformulation that has to have certain Q3 properties. When it's injected, it will interact with subcutaneous tissue, and then eventually it will be taken up by immune cells. So all of those things—will they be looking the same in the generic products? Because of that, we do some demonstrations, and industry really would like published case studies. If you publish case studies, this will be a very highly read paper.

Nitrosamines
Industry comment: "We can eat more nitrosamines in one breakfast than in one year of metformin."

It is a very complex project. It's complex chemistry, complex analytical chemistry. All this raw material and reference standards have to be made. It's a technical problem. The problem is the limit that needs to be measured. There are many aspects to this problem. I think this is one area where so many people work together. It's really remarkable to see. I have some hope in this whole industry by how nitrosamines are being addressed. Come to our workshops.

Drug-Device Combinations and Human Factor Studies
Industry comment: "If a pen would be a pharmaceutical product, we all would be writing with big pens."

You see, every pen is slightly different, for sure, but yet we can write. My son has type one diabetes. I'm a mother of a drug-device combination user. I know exactly how those people are trained. It's a very wonderful community. It's a lot of fun, and we had already two workshops. There are many questions, some around pen injectors and auto-injectors—most commonly used products—some around inhalers and other products, more about how to design human factor studies, and they're never truly identical to the RLDs. So they need guidance for non-inferiority margins and what are the differences.

Bioequivalence and Alternative Approaches
Industry comment: "If some of those generic studies would have to be tested for bioequivalence right now, RLD products would have to be tested for bioequivalence right now, they wouldn't be equivalent to themselves."

There are several products on the market that are just variable. So lot to lot, if you buy three lots, they would not be passing bioequivalent studies. I hear that a lot. But there are many products—give you an example of paliperidone suspension, olanzapine, and haloperidol. Doctors are very reluctant in switching patients from one antipsychotic medication to another. The clinical trials last a very long time, especially if you need the washout period. Normally, just physicochemical characterization of the particle size, zeta potential, dissolution would be enough to extrapolate. Yet generic companies don't like to be trailblazers. They don't want to invest a lot of money and not know what the outcome would be.

Inhalation is another area like that. There are some simple areas—meeting time points due to COVID—and then also orphan indications where there are just not enough patients and very expensive RLDs. The need for harmonization is also very important there.

We will skip intellectual property issues—there's not only Q1, Q2, but dress code and continuous submissions for device design. All of those really impact availability of generic products.

Summary and Acknowledgments

I'll come to the summary. We identify all the same general issues and hear all of those potential priorities for the research. Many of them have been mentioned today earlier.

We have a very good presence. I do not run the center by myself. People who work in the center know that if it were left for me, nothing would be happening. But we have a very nice presence online. We have a website, social media, and YouTube channel where you can find all the historical presentations.

We have this wonderful way of searching websites for GDUFA research outcomes—not only our research, but all the GDUFA research outcomes. Some people have all journal subscriptions and some don't. This is a wonderful way for many of you to find published information, including posters.

Finally, I need to acknowledge a lot of people. First of all, support from the U18 grant to start the center. I need to acknowledge all the generic companies and stakeholders who agree to be interviewed by us and spend time with us. Rob Lionberger suggested creating the center. Sam Raney is a wonderful project program manager for us, and many times he was part of all of those interviews. We have Andrew Babinski, Dan Lee, John, and Shannon Hoo, who are on our oversight committee. Finally, this is our CRCG team. Jim Polli and I run the center together. Vishal Krishnan is the associate director—she really runs everything, not us. Dan Hamil and Jen Dick help us a lot with all the logistics and our workshops. Finally, for the interviews, I had two graduate students and family students participating. This year I hooded one and was in the party of graduation of another one. So the center has been around for a while to even see great students be trained. Thank you very much.

Sam Raney: Thank you, Professor Schwendeman.

Prabhakar Reddy (United States Pharmacopeia): Thank you, Sam, and good morning, everyone. In today's presentation, I'll provide an update on our complex generic activities with a specific focus on the stakeholder engagement activities that resulted in providing some research topics for our consideration. At the same time, we had an opportunity to evaluate the feedback and then propose some new general chapters.

USP's Current Portfolio

Looking at USP's current portfolio of complex products, we have a number of general chapters as well as monographs as shown here. However, when we did the gap analysis, we did find several chapters as well as monographs missing in our portfolio. That made us focus on complex generics.

What we are doing currently: we have a new program unit for complex generics, which is newly created, and we didn't know exactly where to begin with it. As we all know, complex generics is a huge ocean. So we started doing several stakeholder engagements as shown here. I'll come back in a minute. We also have an expert panel currently working specifically focused on complex products, basically for performance tests, and they already published several articles. Currently, they partner with APS to present through webinars for additional industry feedback. We are committed to providing solutions to the generic industry.

Stakeholder Surveys

We did two surveys, one in 2021 and one in 2022. The 2021 was a small survey—only 14 qualified individuals having extensive experience in complex generics. We did one-hour telephone interviews. As shown here, the challenges they mentioned to us: technical, mostly equipment-related, lack of innovative dissolution methods, manufacturing issues. Scale-up is a

big issue. They can make the product in the lab, but they can't go to larger scale. Regulatory guidance, lack of complex bioequivalence approaches. Others are like lack of availability of RLD because some of the products are limitedly manufactured, so it's not available.

For the quantitative survey, we did a global survey. This is an online survey of 356 people. As you can see here, the product support needs: a majority of them, 83%, mentioned complex injectables. That's where they need help. The other things are topical and transdermal, 54%, ophthalmic inhalation. The challenges are here: bioequivalence, we all know that Q3 characterization, extractables and leachables is one big thing which I'm not going to focus on in this presentation, but we get a lot of feedback and requests for guidance.

Complex excipients, nanomaterials, biorelevant dissolution media as well as methods. When we asked about specific focus areas for USP to consider, physical reference standards and educational courses were on the top of the list, along with the complex documentary standards.

Complex Injectable Open Forum

We also organized a complex injectable open forum last year. It was April 25th and 26th. We had good registrations—900 registrations from more than 30 countries. We had several presentations as shown here. The goals were to understand the challenges, both technical as well as regulatory, and to understand the gaps in USP and other compendia.

I summarize the feedback here on the right side. Again, for critical quality attributes, the Q3 physical characterization methods are at the top of the focus. Specifications and types of tests are not available. For dissolution, they mentioned using non-compendial methods. They have been asking us for including rotating bottle apparatus in the compendium. Lack of accelerated IVIVC methods, no guidance for complex products.

The manufacturing challenges are the same. These are product-specific and project-specific, lack of human resources with expertise, scale-up issues. For the general challenges for USP specifically: lack of USP general chapters for microspheres and microzones and also for molecular weight determination. Knowledge sharing is a big issue because of proprietary concerns. Lack of physical standards also for both PLG polymers as well as molecular weight standards, and lack of bioequivalence tools such as in silico or simulation.

India Visit

In September, we visited India. We met with 19 companies from September 5th to September 15th. The locations are shown here. Their expertise is mostly on complex generics. Sixteen out of 19 are working on complex products. One of them is a PLG polymer manufacturer, and the other two are supporting CROs.

I'm not going to go through all the feedback we received, but it was a very good meeting. Two things came up from the meeting: iron colloid microspheres—not only general chapters, but the physical materials—and lack of chapters. I think even the PhDs are helping them, but they say if you have a general chapter, that will aid in further research.

Research Needs Summary

This is essentially the compilation of all the stakeholder engagements, what we heard from them, and I summarize the possible research needs:

1. Development and validation of analytical methods for characterizing polymers. Even though it's been more than 30 years the product is in the market, we still do not have neither standards nor characterization methods.

2. Q1, Q2 sameness, correlation to Q3 and bioequivalence. What they're asking us: how much difference you can have between Q1 and Q2—5%, 10%? But how about if you have a design space and then go to Q3, and still you can get the same equivalence to the brand product?

3. Evaluation of commercially available orthogonal analytical methods. Since Anna has published several papers on iron colloids, there are several methods that have been published, but still I think clarity is needed when to use them. Since there are several of them that are not commercially available also.

4. Development of sensitive and specific particle size characterization methods, especially for complex products, emulsions and suspensions.

5. Identification, validation, and optimization of novel methods to replace the current BE requirements for complex generics, OINDPs.

6. Development of biorelevant IVIVC correlation models and simulations.

7. Establishing equivalent alternative excipients. People are asking if a brand product has a synthetic color, can it be replaced with a natural one?

8. Identification, development, and validation of universal analytical methods for characterization of iron colloids.

9. Finally, there is a big need for multigrade standards to support both microspheres as well as iron colloids.

New USP Chapters

Based on the feedback, we are proposing three new chapters to support complex injectables and drug-device combination products:

Chapter 1155 for Iron Colloid Formulations: We are going to provide all the characterization methods in this one. We just have a prospectus that has been published on the USP website. An expert panel will be formed. If anybody is willing to participate as part of the expert panel, you're most welcome, or your colleagues.

Chapter 1156 for Microspheres: The same situation. An expert panel will be formed.

For drug-device combination products, we already have a joint subcommittee, so the product quality tests will be described in this one. We're going to go with a general chapter first, and then we'll come back based on the classification of drug-device combinations like prefilled syringes, drug-coated stents, drug-coated balloons, etc.

Extractables and Leachables

Finally, there are a lot of requests for extractables and leachables for complex products. With that, we have discussed with our expert panel and expert committee, and they agreed to write three new chapters: 1664.2, 1664.3, and 1664.4, specifically for parenteral, ophthalmic, and topical/transdermal ones. We already have chapters 1663 and 1664.

I think I'm done four minutes before time, Sam. Thank you for your attention.

Panel Discussion

Sam Raney: Thank you so much, Dr. Reddy. I think what we might do is transition straight into the panel discussion. Is that okay?

I think that was a perfect segue, actually. Beautiful synopsis and very nice summary, well-articulated clarity about the feedback that you're hearing on the specific research priorities. One of the things that really came through from your talk—and feedback we've heard from other places too—I think Anna, you were saying this as well—we have these novel characterization technologies, but the approach to validation, the standards for the methods, the equipment for the methods, the compendium methodologies that are ultimately needed to make these efficient in terms of their implementation and assessment ends up being sort of the next stage of that lifecycle from research to developing the novel methods to ultimately having compendium methods for which the endpoints are well-defined, the acceptance criteria are well-defined. It's a long, long time to get to that stage.

We also have joining us online Dr. Tausif Ahmed. What I'd like to do is begin our panel discussion by giving each one of you an opportunity to reflect upon what really stood out for you. If we could just take less than a minute to highlight a couple of things that really stood out for you as being priorities, critical areas that FDA should be investing in research to address some scientific challenges. Dr. Ahmed, since you're online, allow me to offer you the courtesy of the first shot at that.

Tausif Ahmed (Dr. Reddy's Laboratories): Thank you very much, Sam. First of all, I think it's a great opportunity and very intriguing talks. The two things which I want to highlight—it's already been discussed, and that is where the generic industry is also struggling. The first one is on the risk assessment from an immunogenicity perspective. What we would like to understand or have more focused research is: can AI/ML technologies be used to identify the risk assessment or immunogenicity risk assessment? We would also like to have potential collaboration between FDA and generic industry to develop such tools so that this area can be advanced. It is still an evolving area, and we are still on the learning curve. That is the first comment.

The next comment is on—I think we had a full day yesterday on NDSRIs, the nitrosamines—and we also talked about potential drug shortages. What we want to focus the research on is: there will be a big burden on the generic industry if we have to reformulate these products to address the NDSRI issue. So how do we address that risk? How can we avoid the burden of repeating the bioequivalence studies when we reformulate? That is one area we from the generic industry are looking forward to, and we have ideas of potential collaborations where we can advance the science. These are the two key areas which I would like to focus on. Thanks for the opportunity, Sam.

Dr. Pradeep Dabhi (Cutyx Research): Thank you, Dr. Raney, for introducing me. Whatever I have seen in the presentations and discussions, looking at the USP presentation, I could find

that there are only four transdermal monographs available in the USP. I request industry to please donate monographs to USP so that generic industries can get good reference and go for generic development.

The survey also showed that 54% of industries need support for topical and transdermal development. That's a good survey that USP has done. According to my view, the research priorities should include alternate bioequivalence for non-Q1, Q2 formulations for topicals as well as transdermal formulations. Because in transdermal patches, we start optimizing formulation based on the in vitro permeation testing only, and then we need to conduct the bioequivalence or PK studies. I would request FDA to have a research priority on transdermal patches with alternate bioequivalence approaches. Thank you.

William Ganley (Nanopharm): Thanks, Sam. There were some really interesting presentations this morning. Some of the topics that really stood out to me were the need for release methods across a range of different dosage forms. We saw this for long-acting injectables and oral products. I'd like to add inhalation to that list as well, because we've had some research projects in that field. They've borne some fruit, but I still don't think we have a good, well-established method for that. As a research priority, we should probably be working together across these different disciplines to share learnings and make sure that we can generate these biorelevant methods.

I think the same goes for modeling. We heard a lot about PBPK and the integration of in vitro data into PBPK across different dosage forms and different disciplines. Modeling communities can sometimes act in silos a little bit. So again, I think if we're going to look to develop these new in vitro tools, we should be doing them together, and we should do that with the in silico as well.

On the AI/ML stuff, I think I still remain a skeptic about a lot of the applications of these technologies to drug product development. But we heard quite a few times that the synthesis of information across a wide range of sources is something that AI could be useful for. Yesterday, in the panel discussion, I think access and structure and machine readability of all of the data that we're all sitting on was highlighted as a challenge. So if we can maybe do something that's slightly less exciting but incredibly useful and generate some AI tools to solve that problem, I think that'd be a great place to focus our attention at the moment.

Sam Raney: Is there anything that you'd add that you didn't hear that you felt was conspicuously absent that's really a priority? For example, you added the inhalation piece to the dissolution. Is there anything else?

William Ganley: I think inhalation—I will always say that. But no, I think just focusing on common problems across different dosage forms is the key thing. We had several talks yesterday focused on orthogonal methods to characterize inhalation products. Did you feel that adequately addressed the kind of sphere of topics and the research areas?

William: Yeah, I think it gave a really good menu of different potential techniques to choose from. I think the challenge for us would be selecting the right ones.

Andrew Graves (Teva): Thank you. From my perspective, I think that one of the common themes is that complex generics remain complex, specifically with the characterization aspects. Certainly, a topic of interest for me is the immunogenicity perspective. I think some of my colleagues that presented share that view.

I don't want to minimize the fact that a lot of research has gone into immunogenic assessments, and we have come quite a long way. But if I were to try to distill it down distinctly to what I think the research priorities could or should be, it'd be:

First, to standardize where we can—whether that's standardizing the model impurities that we're chasing after and want to evaluate, certainly standardizing our assay sensitivity levels. I think that would be an achievable goal.

Where we can't standardize, we should harmonize. Obviously, we cannot always guarantee that the assays are going to be identical across the industry. But again, I think that if we have some ideal approaches—whether that's published in a white paper or something of that nature—would be immensely helpful to industry to give us an idea of what the agency would be seeking and how best to achieve that.

And then lastly, is to grow and expand. A lot of effort has been put into these particular modalities to try to understand our products. I think that the same techniques and assays can be employed across a broader variety of drugs. That would help, I think, from an industry perspective, to really make this investment that we've made into these assays and into these technologies worthwhile.

Sam Raney: You saw the presentation by Dr. Ravi Shankara. It seemed like some of those things resonated for you. As you think about the specific area, because it feels like there's a lot of work to be done in the immunogenicity space, where would you prioritize? Where would you go first? What do you think are the most critical things to address?

Andrew Graves: From my perspective, I think that there's a lot of appetite to look at recombinant peptides, to look at oligonucleotides. I think most of my industry colleagues would agree that one of the areas of hesitation is: we can do this, but would it be accepted? What's a genuine concern in terms of differences between the proposed generic product versus the reference product?

I think that we're of the understanding that of course, there's going to be some differences in these assets. But there should be a minimum set of standards that we can expect to achieve. What makes it particularly challenging in the immunogenicity assessment realm is that we're typically one of the last things that gets done in the development. So we're working on a team of people who have been working on this for a couple of years, and then we do the assessment. Of course, one of the concerns is we do our assessment, and the assessment says this is a risk, we shouldn't submit this. Although that is a risk, that's an assumed risk from an industry perspective.

What we don't want to have as an assumed risk is: we think this is a great-looking assay, we feel that we validated it, we have all these boxes checked, and then we submit it, and then we get feedback of "well, maybe it's not sensitive enough, or maybe we didn't agree with the statistical approach." Those are the things that I think are, in the grand scheme of things, the low-hanging fruit that we can probably solidify in relatively short order. A lot of research has already been done. My recommendation is just whatever research remains, let's focus on this.

I almost feel like in many regards we've gotten to a point where, because a lot of the answers for immunogenicity assessment have been resolved, there's almost a malaise—meaning it's not the most important thing anymore. It's still an important thing, but because it's not the most

important thing, some of these details can wait. I think I speak on behalf of several of my colleagues here that these are still important facets that we need to explore and finalize to really get this thing over the finish line so then we can fully focus on other problems, other areas that we want to resolve.

Ripen Misri (Apotex): Thank you. I would first like to echo what Andrew just said on immunogenicity, and it has been one of the major pain points in peptide generics development. I think the main issue has been lack of standard assays, lack of guidance in this area. Although we have come a long way, like in the last eight years since the draft guidance on synthetic peptides was published, we have come a long way, and FDA has done a very good job of publicizing some of the research that was done through different workshops, outlining some of the expectations.

But I think there is a need for guidance, a formal white paper that elaborates on what the expectations are. It may be just as simple as stating—because there are so many variables that go into immunogenicity assays, just starting with number of subjects you would need to choose, number of dilutions you need to choose, how many TLR agonists you need to choose, what are the kinds of cytokine panel assays that you need to choose. Some of these can be standardized so that we have a starting point for developing the assays and validating the assays within the industry.

Further on, you might develop a very good assay, a robust assay. But is the assay really predictive of clinical immunogenicity or the clinical risk? That is another area where I think there is not enough evidence or research being done. I think it was mentioned in the previous presentations as well. This could be one of the research priorities: to see if these assays, although they are very good assays and robust assays, are they actually predictive of clinical immunogenicity?

Moving away from immunogenicity, another area that we heard a lot of talks on was characterization of oligonucleotides, demonstrating the API sameness. This is another area of research where I think we need to come up with a panel of orthogonal methods or techniques which would be predictive of the API sameness. There are various complexities to it. As speakers have spoken about, diastereomers, base substitution even during performing the assay. If there could be some research prioritized focusing on developing a panel of assays which would be predictive of the API similarity for oligonucleotides.

Prabhakar Reddy: Looking at the presentations, I do see a lot—I'm not a computer guy, so I'm still holding on that one. But from me, trying to understand the complex generics, the one thing that is missing is the characterization of the final product. Q1, Q2 is okay, people can figure it out. But when it comes to Q3 characterization, that's where we need additional research: how we can correlate the physical characteristics with the in vitro methods.

I do see some presentations today. DGMI, I think, is one of them—technologies like that where you can see the particle without going to the chemical analysis. If you have tools which can distinguish between the various—take an example, PLA polymer. It took 30 years to get the first product. So if we have tools where the industry can look into spectroscopy techniques, can identify the particle diameters, porosity, all other things, if we can establish some kind of correlation to the in vitro methods, I think that's the area where industry is going to benefit quite a bit.

Anna Schwendeman: Let me give a plug to Marina. I thought it was a wonderful presentation, and it's actually something that we don't address but goes across from OGD and other parts of the FDA. We don't have a good model for injection, subcutaneous injection. Yet you inject the LGA microspheres—there is immune response, and then sometimes fatty acids get in and other things get in. You inject long-acting sustainers—they clump together. Sometimes you also have immune response. Sometimes they dissociate. You inject COVID-19 vaccines—they don't stay as nice, beautiful balls. They all fall apart, and then you have to get the cells in. You inject insulin or GLP-1—they start aggregating right there. Tissue interaction. We really do not have a good model. We want this kind of model.

Also, it goes further. Monoclonal antibodies the same way, new products. What is the bioavailability from the local injection? My understanding: we're all trying to figure out how to predict aggregation, local aggregation, tissue interaction. This is a wonderful area of research that, with new technology, is needed. Yet we do not have it. I think this is one area.

The second small one: we are all suffering from the lack of globalization, global approaches to assessment of the products. Many times companies spend so much more money and trials to do it. We understand it's very complicated, but we all live in one global world. We all worry about climate change. So we want to have some reusable cartridges for our auto-injectors. We want global warming propellants that don't affect global warming. Yet we are also spending a lot of money for extra clinical trials. We are buying more RLD. So if we, as FDA, together with EMA and many other geographies, could work on that, that would be really wonderful for global health.

Thomas Tice (Evonik): Let me start with the long-acting injectables which I spent some time on. I think any techniques that we can use to simulate the performance of these long-acting injectables is worth going after. I don't know if we're going to reach this ultimate goal of predicting IVIVC. IVIVC is very difficult. I know one long-acting injectable—they have 30,000 data points for a product on the market, they still don't have an IVIVC.

But I think for development, it could be helpful to do that. In fact, we are aware that some in vitro release testing—you're actually changing the performance of the product when you're doing the testing. That's not good. So Marina, what you're doing is pretty interesting.

You do need to keep in mind that long-acting injectables—there's all kinds of suspensions. There's these LG polymers (that's the USP new name for these polymers, by the way, LG polymers), and then you have microparticles, and you have implants in this field, and then you have local delivery. You have sinus delivery. You've got products in the knee, ocular delivery, various routes of administration ocularly. So there's all kinds of simulations that could be done. You may not get all the immune responses unless we get organoids to help us out from that standpoint. But this is not final product testing release—I'm talking about development, so you can get your progress moving as quickly as possible.

What I did not see—I'm sure we've done a lot of research in that area—but I would like to remind the audience that these complex parenterals are product-by-process. So you can have a perfect Q1, Q2, and as I spoke last year, you could have three generic companies start with three different LG polymers and end up with the same Q1, Q2. So you have to—that makes things a little more complicated. So if you do research, it'd be nice to align that at some point where you can compare what your results are based on what the process was.

That's the kind of things that DGMI could do too—that you have that potential to do that with the structure analysis. But the big part is, there's a lot of companies that have made perfect five-gram batches. So it could be interesting to have a program: how can you simulate scale-up? How do you do scale-up at small scale? Maybe that's a challenge I'll throw out. I think a lot of these, especially the performance testing—because that's really important. You can make all this stuff, but you just can't make a release test, and the PKs are pretty convoluted.

I think maybe AI can help in that spot. Maybe we can smooth out where we need to be on PK and not exactly have every little wiggle in the curve. We'll see where we go from there.

I think also, any time you can improve the analytical—there's products on the market. 1986 was the first long-acting injectable. There's still no generic to that. So I'm sure there's ways that we can analyze these products and make them better from the generic standpoint. Obviously, we don't want to make them better, but at least from an impurity standpoint and purity profile.

Sam Raney: That's a very nice platform to now transition to our FDA panel. Perhaps Dr. Yan Wang can pick up right from where Dr. Tice left off, and I'd be interested in your perceptions too about what really stood out for you as the research that was needed.

Yan Wang (FDA): Sure. Thank you. I think, first of all, all the public comments do cover a wide range of scientifically very interesting topics. Just based on my personal research and regulatory experiences, my top three:

First, we need to explore analytical techniques for characterizing complex drug substances like oligonucleotides.

Second is immunogenicity assessment for peptides and oligos.

And last, but not least, which my heart goes to, is the characterization of complex formulations.

Here I think there are two sides when we talk about generic development. The good thing is you already have a product out there that you can get your hands on, you can characterize it to understand it. So here, I think, in terms of research, what we do is we try our best, at least to make sure at the end of the research we have something that can be readily applied to either support product development or be implemented in our guidance or our regulatory assessment.

For complex product development, for long-acting, for instance, microsphere products, there could be two strategies, and we are working toward trying to really understand the formulation so we can ease the burden from the clinical side for bioequivalence to the in vitro. Here there are two ways. One thing you could say: if you want to develop an in vitro-based bioequivalence approach, for instance, how can you bypass the biorelevance IVIVC, which I think is very critical? But I think that is one way to look at it.

Here, potentially, there are two strategies. One way is you actually look at the product, you really characterize it. If you have the tool—so that's why we have been heavily invested in exploring new analytical tools to understand the polymer, which I think we have made significant progress. It's really interesting, and I appreciate USP's survey to see there are apparently still gaps in that area in terms of polymer characterization, which I think is worth further looking into to make sure we tie the loose ends.

Since the last decade, we have made a lot of progress. But then, with the advanced imaging, AI-assisted characterization, we'd be able to really understand the inside structure of a formulation, then identify those CQAs to know what would be their impact on the release. So that's one way you can go to develop your product.

But then the other way is to develop this biorelevant dissolution method, which can be challenging. But what I think the real value there is that, coupled with this characterization-guided development, can really let us further explore the design space for products. Like Tom mentioned, the product-by-process, and step away eventually from formulation sameness.

Eric Pang (FDA): I'll be quick. I totally agree with Andrew and Ravi Shankara about the need for us to publish and make it clear on some of these immunogenicity studies in terms of what the expectation is. Part of the discussion, I think, can also occur at the—again, the CRCG is hosting, we're hosting with CRCG, the workshop on immunogenicity study in October.

I think the discussion and the results from that, we can start drafting a white paper after that and potentially having a guidance. In terms of additional research into this area, I think one study that we should be thinking about is how well these individual immunogenicity studies correlate with what we observed clinically as well as real-world evidence. I think that will be the next step to think about, because for us to make some of these regulatory recommendations, it really depends on how well these studies correlate with the actual results.

One thing I'd like to say about the AI and ML, which is a very hot topic right now, is that I think these can actually be used for real-world evidence. Real-world evidence can actually be used for some of these products that were approved in the older days, where not much of the clinical studies were there to demonstrate the immunogenicity risk. I think having these tools to help us analyze products' immunogenicity risks will be very helpful, especially given what we already know about how well it works in the real world.

Meng Hu (FDA): My first comment is about the complex APIs. This morning I heard multiple presentations talking about advanced analytical approaches and followed by the data analytics, especially multivariate data analysis. But we all know that for API sameness, very few samples will be used, but each sample may produce a huge amount of features by, let's say, NMR data or LC-MS data. I think there's a research opportunity over there. With such a type of data, usually we call it large feature data, meaning the number of features is much greater than the number of samples. How can we produce meaningful and meaningful results and evidence in such a situation that can really support the decision-making? That's the first point.

Second is about the AI and machine learning. Today, including yesterday's session, I heard multiple presentations talking about utilizing AI machine learning to streamline generic drug review processes, especially for some steps where we can even automate the process. I also heard Dr. Ganley's opinion about AI.

To my observation, currently AI's demonstration, especially those fancy features, is mainly for entertainment purposes, which means if there are some hallucinations, we will just smile and say it's still not smart enough. But we are doing business and work for human health. So we should really take very careful steps with caution using AI.

Back to the topic, I think in order to—but I think really streamlining the generic drug review process based on AI technique is a trend and the direction to go. We need to—there are multiple layers of work that need to be done before we really talk about that.

For example, as ChatGPT just appeared or was announced, we actually asked ourselves whether ChatGPT is suitable to process regulatory documents or review documents. Then we did a preliminary analysis. We tried to use ChatGPT to analyze public drug reviews, for example, for full prescribing information content. We see whether ChatGPT can generate full prescribing information content in the drug label based on the review content. The result seems very promising, but although it's like that, we still need to take very careful steps for the following kinds of work.

For example, how can we utilize—let those language models or AI models be more domain-specific? Because the general model is trained by general documents. However, we need the AI model to be more familiar with our specific domain contents. So I think what I'm saying is it definitely is a good direction to go, but there's a lot of work to do.

Cameron Smith (FDA): With the oligonucleotide products looming on the generic horizon, I see a large opportunity there for research into characterization of those API sameness characteristics. A number of these oligonucleotides have multiple diastereomers, as was highlighted in a number of the talks, and I see that as a very large challenge to solve. Obviously, that would be useful for API sameness, but also for ensuring manufacturing consistency throughout the product post-market lifecycle.

The immunogenicity risk for the oligonucleotide-type products—also, research could be conducted to better understand what those risk factors are and whether or not things like characterization of the impurity profile might be important in sort of indirect risk mitigation of some of those factors.

The other thing I would say is for the innate immune response modulating impurities, we could potentially have some better characterization of those innate immune response modulating impurities from the analytical chemistry standpoint, and again, that could also potentially help—that could be an additional way of mitigating that risk in addition to the standard innate immune response modulating assays that we've been talking about.

Daniela Verthelyi (FDA): This has been a very interesting session. I think that we've talked about very different things. We've talked about low-hanging fruit and things that we can immediately do to improve our access to drugs, particularly having to do with immunogenicity assessment. Whether it was from Teva or others, there are very concrete steps that can be done, very doable things that can be improved. That's really helpful.

But we've also discussed some more sophisticated techniques. The idea of looking at skin and subcutaneous tissue and how products really behave in people, how they interact with the immune system, is very interesting. The idea of looking at organs-on-chip and doing that kind of analysis. The idea of really getting a much better characterization of impurities in oligos. I think that's an area that really needs to grow. All of those are really very promising.

I want to emphasize the need for all these to really link with clinical relevance, which is our ultimate goal. But it's so hard to do because we don't have the data. I would also like to link that maybe not with AI, because AI seems to me to be too much of a pretentious word, but just with computational modeling.

I think that there's a lot that can be done, a lot that can be achieved. But I really worry about the quality of the data that goes in as being fundamental to the quality of the data that goes out. As

a community of scientists, we need to reach some sort of agreement as to what it's going to be—that litmus test for the data that goes in. That's going to be really hard work that we're going to have to do, on both sides, to really come to an agreement about what we can use, what data is available, what data is public, and what standards of quality of data we can use. I look forward to continued discussion on those issues.

Deyi Zhang (FDA): I'll probably talk about the complex APIs. Complex APIs certainly contain many different classes of drugs. But in this workshop, we focus mainly on peptides and oligonucleotides. Since we already discussed a lot on the peptide side, I'll probably focus more on the oligonucleotide drugs.

Certainly, for those types of new class of drugs, I think the active ingredient characterization, impurity characterization, and also immunogenicity assessment are some of the key areas that probably need more research.

I echo the other commentators' and panelists' comments that it will be good to have a panel of assays that people can use to characterize oligonucleotides. But oligonucleotides, certainly, as we see this morning, we are definitely not there yet.

In terms of research areas, I think one is to explore or see the application of new technologies like what we mentioned this morning—the NMR, vibration spectroscopy—whether it can be applied to oligonucleotide characterization. Also, another direction may be innovative approaches or applications of known technology. For example, the ion mobility—like Dr. Jones's research—whether you can use that as an attribute to study, to understand the diastereomer impact on those ion mobility data.

Recently, in the TIDES meeting, I definitely saw a presentation where people use RNase T1 to get different fragments and use that fragment as an LC-MS method to study the minor differences between different diastereomers. So those, even though LC-MS method is not something new, but how to innovatively apply that method is something that I think FDA can support that research.

In terms of impurity characterization and immunogenicity, I know certainly these areas are even falling further behind the peptides when you compare oligonucleotides with peptides. So those are areas that we definitely want to have more resources.

Lei Zhang (FDA): Thank you, Sam. I'll probably focus my comments mainly on the oral products since the others have been covered. Because we all know oral products—the majority of products are oral products. We have done a lot of research since GDUFA I, and Rob also mentioned there's the main area for oral products, mainly for efficient bioequivalence as well as global harmonization, because we know M13 is going to be implemented sometime later this year, focusing on immediate-release products. The next product that will be harmonized under ICH is the modified-release product.

I'm very happy to see some of the public comments focusing on extended-release products as well as delayed-release products to see what could be the knowledge gap, especially. But I didn't really hear from the industry what's the most challenging area they found in terms of the global development of a drug product. We probably should focus research on those areas to help harmonize and also address the research questions to see how we can utilize more standardized ways to characterize those products.

But we do hear from public comments on those biorelevant dissolution methods to help make them more predictive, also to help assess maybe food effect even for the extended-release products. Currently, for oral products, especially if they're systemically acting, you can always conduct a bioequivalence study, but we also always look for where we can do waivers for additional strengths or some other conditions if we don't have to do the human studies.

Another area also very interesting here is about the post-marketing surveillance, how we utilize the powerful tool about real-world evidence and data. I'm also thinking maybe not just only the US data, but also maybe other country data, because they have different medical systems. They also have a lot of real-world data there. Maybe we can think about how we can have more global collaboration. Of course, the research is the tools we have to—hopefully, we can utilize the evidence already there to help address our questions.

Another topic I'm also very interested in is the reverse engineering talk. How we can help the industry, because I know a lot of generic companies say, "I don't know whether my product may be different from the RLD," and because for the immediate-release, we also have high-risk versus non-high-risk. I think if they can utilize those tools, maybe it can help them determine whether they may have a risk of the non-bioequivalence in the fed condition versus the fasting condition.

Sam Raney: Well, I know that we're all ready to go to lunch. But I did want to ask: was there anyone who had a question for one of the virtual public comment presenters? Because that would be our opportunity to ask that question. They're able to raise their hand, and we can unmute them. Were there any questions that you wanted to ask them?

If not, then I can't thank you enough for staying with us all morning and for your engagement. Thank you very much to all of our public comment presentations and to our faculty presentations. This has been incredibly valuable in terms of being able to crystallize out what the priorities really should be and the specific scientific challenges that we need to address. With that, I'll say enjoy lunch, and we should be back here promptly at 1:30. Thank you so much.