FY 2026 GDUFA Public Workshop – Day 2: Edited Transcript

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Session 5: Leveraging Generic Drug Industry Expertise & Insights for GDUFA Research & PSG Prioritization

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Moderator:

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(talking)

Giuseppe Randazzo, MS: Good afternoon, everyone, and welcome to the anchor session of this year's public meeting for GDUFA Regulatory Science Research. I would like to thank FDA for inviting us and our colleagues here today and yesterday. So far, it's been a really good session and a really good couple of days. So this one, this session here is again the anchor in leveraging generic drug industry expertise and insights for GDUFA research and PSG prioritization. We had a lot of talk already on PSGs and we'll talk and dip our toes in the pool a little bit in this session, but hopefully talk more about the impact and how industry can work with FDA to a greater degree when we think about the research that's hopefully going to go on here through this program.

So the way this session will work out is we have 6 presenters, I believe 5 are virtual, and of the five virtual presenters, they're going to give a presentation of about 4 to 5 minutes of concepts, ideas regarding research. After each presentation, we will open it up to the panel to ask questions, see about the validity of the research, any thoughts about the research. And then finally, at the last presentation, before we get into the second half of the session, will be an in-person individual to speak on their research concept and research idea. And then again, we'll open up to the panel for that as well.

Before we get in between those two, whether it's to start off with the research concepts, research ideas, panel conversation, Sam and others are going to talk about and set up and tee up the second part of this session, which will largely be a roundtable of questions and answers from the panel on, again, how do we get better in operationalizing some of the concepts, ideas, and operationalizing how industry can get more involved potentially with stakeholders such as CRCG and FDA when it comes to this program. This, of course, is a

very, very nice way and good start. We do this meeting once a year, thankfully for Sam and Rob, to put this together once a year. And this is a really strong way to start that conversation. And this is one input that industry has regarding how they can have a voice in the research concepts. What we want to talk about again the second half of this session is what's the next steps? How can the industry get better involved in ideally helping out the FDA with some of these ideas? So with that, I'm going to, and I don't know how to do that Sam, I want to start the virtual presentations. Ok, I can just for it to happen, and it'll happen. So do we want to start with the first virtual presentation, please? Look at that, very good.

Public Comment Presentations & Panel Discussion

Virtual Presentation by Raghu Ram Pannala, PhD

Greetings, everybody. My name is Raghu Ram Pannala, representing ScieGen Pharmaceuticals Inc. with support from Pharma Reach LLC. Today, I am presenting a practical regulatory innovation concept: expanding AI and ML in generic drug submissions. The intent is not to replace regulatory quality, CMC, or bioequivalence expertise, but to strengthen review readiness by identifying dossier inconsistencies before submission. This approach is FDA-aligned, CMC-focused, and built around a human-in-the-loop concept. This is a standard disclaimer.

First Cycle Review Readiness Challenge: The core challenge is that many ANDAs continue to receive deficiencies during the first review cycle. These deficiencies often arise from unresolved CMC, bioequivalence, and dossier alignment gaps. Once an application receives an IR letter, DRL, or complete response letter, the impact can be significant, including delayed approval timelines and delayed patient access to affordable generics. The opportunity here is to move risk detection earlier before the application reaches FDA for review.

M3 versus M2.3 Alignment Gaps: One of the most common technical risks is misalignment between M3 and 2.3 QoS. In practice, dossier development is often manual, iterative, and spread across multiple teams. That creates transcription errors, omission errors, data drift, and inconsistent cross-references. Key trigger points include batch record information to BE study design alignment. If not corrected early, these gaps may become regulatory deficiencies.

Automated Digital Audits: The proposed solution is an automated digital audit framework using a multi-agent retrieval-augmented generation architecture. The workflow starts with an ANDA dossier, retrieves relevant source content, performs agentic comparison, and

then routes findings through human-in-the-loop disposition before generating an audit report. From a regulatory perspective, this supports expert judgment. From an IT control perspective, it requires source retrieval controls, prompt governance, version control, audit logging, and human review before acceptance.

Explainability by Design: Explainability is the foundation of regulatory acceptability. This slide shows an FDA-aligned seven-step credibility framework. Importantly, this framework retains ontology-free design and full credibility. Each output remains linked to the source passages, rationale, and reviewer disposition.

Three-Phase Pipeline Implementation: Implementation is organized into 3 phases. First, specialized agents are deployed. Second, the system is designed for eCTD readiness. Third, continuous prompt optimization improves precision. The key message is that it's not a one-time AI tool. It is a learning audit framework supported by human regulatory expertise.

Let us have a look at a model audit report which we ran in an ANDA. It links each finding to a finding ID, module location, source citation, risk category, AI rationale, human reviewer decision, and final disposition. This report is not simply a list of AI observations. This gives regulatory teams a structured audit trail before ANDA submission. It also helps management understand which issues should be retained, omitted, monitored, or remediated before the application is submitted.

Next is case Study One: Product A, IR Tablets: In this first case study, the AI system initially flagged 20 potential issues. After human-in-the-loop and temporal filtering, 15 were omitted as legacy or contextual artifacts. These omitted items were not ignored; they were documented and removed because they reflected expired batch references, outdated stability time points, or historical information that no longer represents the current submission state. Five true deficiencies remained, and those retained findings matched with the actual FDA findings in the case study comparison.

Next comes Product B, IR Tablets: Before optimization, the system flagged 8 findings, three major and five minor. Some findings were later removed because they were associated with historical batch expiry dates or outdated stability references. This demonstrated an important lesson: legacy applications require timeline-aware prompt logic and expert regulatory review before AI findings are accepted.

Results and Validation: After prompt refinement, the eight initial findings were reduced to three true deficiencies. Omitted results were false positive temporal artifacts, not current submission deficiencies. Importantly, all three retained matched actual ANDA deficiencies.

Fine Tuning and Oversight: The central principle is that human-in-the-loop oversight is not optional. It is the control layer that makes AI usable in regulatory science. AI brings speed, consistency, and sensitivity in detecting potential dossier risks. Human experts bring judgment, accountability, and regulatory meaning. Regulatory professionals must validate findings.

Looking Ahead: The opportunity is to advance this multi-agent RAG audit framework as a practical pilot aligned with the FY 2027 GDUFA and CDER's broader interest in responsible AI and ML adoption. The next steps are strategic alignment, iterative pilot programs across legacy and new ANDAs, and development of standards for human-in-the-loop validation, audit trails, prompt governance, and source citation. The goal is simple: fewer first cycle deficiencies through a supported human-validated pre-submission audit. I thank FDA for letting me speak in this forum. Thank you all.

Giuseppe Randazzo, MS: And thank you, Raghu, for going first. We'll just spend a couple of moments here to talk about this. Any just general thoughts about the presentation? You know what, actually, I didn't get a chance to introduce all my panelists. They've got really nice bios that you guys have written down in front of you, and many of them have been introduced before. So what I'm going to do is, instead of reading that and spending a lot of our time, I'm going to ask each panelist to say their name, where they're from, and give you a brief break. A brief background. Thank you, Uwe.

Uwe Niesner, PhD: If I had known that, I would not have raised my fingers. So, my name is Uwe Niesner, based from Germany, work for Viatris, and I'm leading the teams for regulatory covering the respiratory, the dermatology, and the biologics portfolio. And I like the idea of using AI-assisted verification of the Dossier content. We saw some other concept earlier today, yesterday, and this one here seems to be to align what I understood to align the batch records and so on with the dossier output. That that is definitely a helpful tool, because transcription errors will happen. In terms of the wider acceptance, of course, it needs to be very clear that the AI agent, if it finds a deficiency, usually it's too late. So such tools cannot prevent you from having a very well thought through agency interaction, a strategy, a development strategy, and possibly such AI tools could be also helpful in the earlier development phases, not only at the output of the dossier once it's close to submission.

Giuseppe Randazzo, MS: It's very helpful, sir. Very helpful, sir. Thank you. Any other thoughts or comments?

Robert Lionberger, PhD: Yeah, so I mean, my sense is that this presentation is from someone working in the company that makes submissions to the to the FDA to the FDA,

and you know, I think you know, like we want you to send us better quality submissions, and so are there things that FDA can do that makes things like this more implementable for you on a company level or at a sort of enterprise or community level, are there, you know, are there things that you know, about the system or methods for doing it or formats for information that can make these methods more reliable. If we want to, you know, encourage companies to develop these tools, what's the sort of role for FDA or FDA, you know, in the theme of the sessions or FDA interactions with industry as a whole to say, look, we want to be able to check our applications submissions with AI tools for common deficiencies. How can we make that sort of process work better?

Giuseppe Randazzo, MS: Right. And I'll extend on Rob's comment. Thank you very much, sir. Is, you know, are there any ideas or thoughts around how we do some research around this, right? So the idea here is we're here for two days to think about regulatory science research. Is there some concepts about what kind of research should we do around this, if there's research that makes sense, of course? And then to Rob's point, that research with the regulatory impact, it helps the FDA, it helps industry along the lines of what Rob was talking about. So that's the theme of the second session is what kind of research can we put forward when you hear these types of presentations? So thank you very much. Any other thoughts? Jim? Yeah, introduce yourself, Jim.

James Polli, PhD: Oh, my name is James Polli. I'm a faculty member at the University of Maryland and co-director of the Center for Research on Complex Generics. So the thing I got from Rob's comment is reliability. And I mean, I don't use AI that much, partly because I'm not sure if it's truthfulness at times. And a little story is I have a brother who works in the industry, and he worked on a drug, and he did some AI on that drug, and it said that I had worked on the drug when I had not. We share the same last name, we don't share the same first name, and it said James Polli. So, as far as research goes, I think this issue of reliability would… which I think is what Rob was harping on. Yeah, reliability research sounds important.

Giuseppe Randazzo, MS: It's very helpful. Thank you, Jim. Any other thoughts or comments? Sir, please.

Uwe Niesner, PhD: It doesn't directly relate to the research, but I think what is very important first, industry needs to make the homework, because when you work with a very wide supply chain, there are very different formats of documents and source documents. So in order to probably, for these tools to be very effective and error-proof, it would need to have a certain standard of input documents, source documents. I think the CTD output is relatively straightforward, but the various source documents, reports, scanned images,

very different templates from different vendors, probably that I would think could be the the difficulty in implementing that across many companies.

Giuseppe Randazzo, MS: That's helpful. Thank you. And as we go through to the other, yeah, we got one more comment. Okay, Brandon. Brandon, introduce yourself, even though you've been up here before.

Brandon Wood, MS: Yeah, hello everybody. Brandon Wood, Teva Pharmaceuticals. I lead the submission and life cycle management for US complex generic products. I think I've had a new term, you know, introduced over the last couple of years, but there's, you know, there's general review friendliness of our documentation, but then there's AI friendly review considerations. So I think one thing that could be, you know, helpful is continued standardization of the way that the information is presented in our applications, templates, etc. And, you know, in general, I think that may help to give us additional tools to pick from as we're doing our internal development. It's a really challenging space because I think in a lot of scenarios, there's, you know, rapid launches and then continued evolutions that happen really quickly. And, you know, it's not necessarily where you want to be in terms of an established regulatory information mechanism system, but I think focusing maybe some research on the tools and, you know, maybe templates that can be AI friendly would help in enabling some of these systems to remove possible error that can come about.

Giuseppe Randazzo, MS: Thank you very much. And I would invite others, as far as not only the panelists, but the public, but the panelists immediately, as we're going through these, if something strikes you as, you know, this is something that can be a priority for regulatory science research through this program, feel free to make comments on that as such. But I also invite it more openly to the public here and beyond online, as you potentially submit comments to the docket to think about the prioritization of research as well, whether it's these presented here. It's helpful for the FDA when you think about research, how certain things should be prioritized, or what maybe they want to look into with some more depth. With that one, I think it's probably time to go to our second presentation.

Greetings, everybody.

Virtual Presentation by Amin Rostami, PhD

Good afternoon, everybody. My name is Amin Rostami. I'm Professor of Systems Pharmacology at the University of Manchester and also am Chief Scientific Officer for Certara. It is a great pleasure to be with you, albeit online, and share some aspects of unresolved issues relevant to applications of the PBPK modelling in this space of generics.

The details of what I'm going to talk about, actually, they are in this particular paper with regard to the unresolved issue of incorporating within subject variability into the PBPK models, which is an essential element of, as I will discuss later on, to assessing the bioequivalence within the generic space.

For those people who are not familiar with the PBPK, I think suffice to say that over the last 25 years, the applications of PBPK in the pharmaceutical space has superseded the traditional space of the toxicology, and this particular paper using AI can help you to look into some aspects of that growth. One thing that many people do not realize, the applications of the PBPK, they are not anecdotes in certain areas, but when a model starts at the beginning of the process, even as early as discovery, the team uses that model again and again for different indications throughout the life cycle. And the example that I have put here comes from our Novartis colleagues, and people can actually study that. This helps also to understand why this idea of the model master file, which came via the colleagues at OGD office is so appealing because we can reuse those models also for the generic space with some additional elements that I will explain related to the within subject variability. Again, those people who are not familiar with the model master file idea, they can refer to some of the reports from the previous workshops as I have highlighted here.

The recent publication by colleagues at AstraZeneca, in fact, highlights that how the elements of recovering the variability can help also with verification of the PBPK model in general. The examples that we have used in the area of recovering the potential sex effect that they are highlighted in this particular paper.

Let me for a second just remind what the source of the problem is. If you are assigning for these virtual individuals distribution of parameters that they are independent of each other, they are assigned from the distribution of, for instance, height and weight, you may end up with a person that individual space looks like a cucumber, another person like hamburger. Because we know the correlations, therefore we have to be actually selecting on the basis of the available information on the correlation side. And this has been happening in anatomical space when we put all these different parameters that they have got linked to body surface area and so on.

However, when it comes to the biology, the correlations between different biological factors and physiological factors are not very well known. And we started on this on the enzyme side, you know, because of the DDI and other issues and recovery of the variability several years ago, when we reported on the same sets of the individuals, having many, many different enzymes that we had measured. And therefore, we started, this is obviously three-dimensional, but it is multidimensional in reality, that we are getting from a matrix that has got all these correlations and possible values in the set.

When it comes, however, to the space that's related to the roots of absorption, for generics, for instance, for the GI tract, all the values that we have got, for instance, for stomach emptying time, the level of the bile salt, the level of the transit time in the colon, et cetera, all of them, they are coming from independent set of studies in the independent set of individuals. And therefore, the correlations between those are not known. And this is a big area for investment because the PBPK models for generics, in fact, they are, as I said, they are at higher level than those that they are used in the innovative space. Thank you very much for your attention.

Giuseppe Randazzo, MS: Okay, thank you very much. And I open up again to the panel. Any thoughts?

Robert Lionberger, PhD: Let me ask our industry representatives about what would make, you know, I think one spirit of this talk is what would make modeling and simulation approaches more useful to the generic industry in pharmaceutical development? Is it, oh, there are more, you know, what's the factor that would lead to their being used more broadly? Is it that they can drive, you know, replace in vivo studies, or they can help you make better development decisions. What's the driving factor that I think will help us understand, like, you know, because this approach here is very important to, if you want to do virtual BE studies, if you want to do a simulation of a BE study and see what would happen in the actual study, this is the kind of thing that you would have to do to have more reliable results in that way. So how important is that to the generic industry and how you use and plan studies?

Giuseppe Randazzo, MS: That's helpful, Rob

Robert Lionberger, PhD: It would be helpful to us to help understand how this fits into the other things that we're doing.

Giuseppe Randazzo, MS: Thank you. Any thoughts? I'm about to take one back for you, Rob. I can tell you one thing, you know, years and years ago, I know when I spent some time here at the FDA, I think one thing that my guess is some of my colleagues here in the industry side would be to have some of those conversations with you guys regarding what are going to be the requirements, what are some thoughts when you consider certain modeling when you think about a development program, what's going to be acceptable to the FDA, for example? So that's something I'm sure that would be helpful to have these conversations prior to the development or around that time.

Robert Lionberger, PhD: Yeah, you know, in an application-specific context, that's an appropriate topic for a meeting to say, I'd like to use this approach instead of using a study, and then ask that question, you know, at the right time, so there's enough time to actually

do that and get to the submission point that you want. But that's something that we're certainly, you know, through our meeting processes, we're willing to engage with in the discussion of, you know, is this approach going to be fruitful based on the current technology and in the context of a specific application. But here it's a little bit more broader question about what are some of the gaps and things that you would like to do with quantitative medicine, but maybe you can't because the tools aren't advanced enough to do that, or FDA hasn't accepted them yet, or you want to sort of see more proofs of concept before, you know, that's I think something we'd like input on for the research activities.

Giuseppe Randazzo, MS: That's helpful. Thank you, Rob. And again, I invite to, if not now, and Jim's going to go, but if not now, of course, the public comments section, public commenting period would be helpful to have the FDA receive some comments on that. But Jim?

James Polli, PhD: Yeah, I mean, just from just collective recollections over the years, I would think one area of application would be where it's expected there'll be maybe a lot of subjects. And sort of, I'm trying to answer your question about, you know, trying to run a study and see whether, you know, what's the sample size that's needed, right? Because that sample size can be impacted very much by the within subject variability. I do think the challenge, though, in this approach is just getting good estimates of the variation, right? I mean, quite often, you know, I was thinking, someone said something the other day talking about the variation in bile salt levels, you know. I kind of wonder how much of that we actually know. So just parameterizing, and that's just one example. Parameterizing is just a huge experimental problem.

Robert Lionberger, PhD: Yeah, and I think the challenge that I think this talk is talking about is certainly you can measure, like I can measure in an individual like different bile salts concentrations and I can see what like look between individuals is the difference. But like in the example here, it's that correlation between the other factors. How is that correlated with other covariates, so you don't end up with a cucumber and hamburger, you know, someone with the extreme amount of bile salt and then, you know, another extreme amount of GI fluid volume that are sort of inconsistent with reality, but both are just, if you sample from the distributions independently, you'll get that. And you know, you know that some of these things are correlated with that. I mean, that's, you know, again, that's a research sort of topic. And, you know, the goal here is to sort of understand, like, how valuable success for research in these areas will be to the generic industry. Will this sort of enable us to, you know, not do more studies because we have better models of what might happen in those studies? Like, that's the ambitious goal.

Giuseppe Randazzo, MS: OK, please.

Uwe Niesner, PhD: So definitely to use modeling that is not validated or approved or accepted by FDA is a high regulatory risk. And the bigger the decision is you make, whether it just defies a specific development decision is a different thing, whether you would like to skip prescribed, PSG prescribed PK studies through your model. So it really depends on the model. But I would think that if at all major companies, but at best, these could be research in projects through CRCG or others to develop these models, because usually you require quite a few PK study or clinical studies to validate your model. And I don't think that many generic companies would have the tools and the resources to do so. So these modeling is, for me, really an important aspect to invest research in. And for me, essentially, it is the vision long-term to replace studies, clinical studies with good validated models, but we are not there yet, so it's a research topic for sure.

Brandon Wood, MS: Yeah, and I would just add, you know, you hit the nail on the head. I think, you know, part of the lack of uptake is likely related to the very high bar that is required for the validation of the model. And at some point, unless it's a question that cannot be answered in other means, a lot of times the resources and economics of validating that model are offset by an alternative approach that while it may not be using the modeling approach, it's still answering the same questions, so I think that is one of the realities.

OPQ Pharmacologist: I believe also...

Giuseppe Randazzo, MS: You got to introduce yourself, sir.

OPQ Pharmacologist: I'm sorry. I'm a pharmacologist and Office of Product Quality, Pharmaceutical Quality Research. So I believe PBPK modeling is a very powerful tool. Once it is validated and we have a credible model, we can use it to develop a patient-specific quality standards. So instead of just using quality specifications just to show like unit dosage uniformity, we can even use it to justify any changes in the product life cycle and justify the need of PK study to be done in certain cases. So it may be a very powerful tool once it is validated and it is capable.

Giuseppe Randazzo, MS: That's helpful. Thank you. Yes, one last last one, Arti? You got tell the folks who you are, please.

Arti Patel: Oh, yeah.

Giuseppe Randazzo, MS: Yes, thank you.

Ms. Arti Patel: Myself, Arti Patel, I'm a senior manager at Cosette Pharma, and I'm leading the regulatory team from the development to submission and approval of the product. So, PKPB modeling more into the development or in the new drugs submissions or ANDA. I

would say it could be right approach or a right place could be post-approval changes because we have already established safety, efficacy, quality and everything. And if we say this proof of concept is successful, then we can try with the post-approval changes for the modified release to this form and delayed release, where we are ending right now, we are ending having the bio study and it can be replaced by this tool.

Giuseppe Randazzo, MS: Thank you for the conversation, folks. In the interest of time, let's move on. Oh, I'm sorry, there's a public comment. Please.

Claire Butler, PhD: Sorry, just one question for myself. So Claire Butler, I introduced myself earlier on in the last session, panel discussion. I'm just wondering, with respect to the PBPK modeling as being an optional tool for establishing the BE in PSG, say, for respiratory products particular. I don't want to trivialize the validation of PBPK models because like it's been mentioned, like has been mentioned, you have to conduct the clinical studies to validate these, right? But I think it's somewhat more achievable to validate the PBPK models for use in de-risking PK studies, i.e. conducting virtual trials.

With respect to the lung deposition models within these mechanistic modelling platforms, my question is, you know, have there been any further research outputs to establish a standardized approach for validating such lung deposition mechanistic modelling platforms? Because I think it was mentioned last year that it was a research focus from the perspective of the FDA. You know, I know there's been suggestions to use scintigraphy studies and CFD, but there are significant gaps there in terms of comparing apples to apples and 2D outputs versus 3D outputs. I know from experience there's, you know, there's still a gap there. So just a question, have there been any further research outputs on the lung deposition modeling?

Giuseppe Randazzo, MS: Oh, we have, thank you very much, sir.

Ross Walenga, PhD: Yeah, Ross, FDA, so I guess I can just respond directly to that. We have a grant that's in progress right now. They're going to be conducting a PET CT study for quantifying lung deposition. So we're hoping from this study to develop a method where you can not only measure the central and peripheral deposition, but also begin to quantify deposition on a branch level. So that's in progress right now. And internally, we've been working on the CFD model that we hope to publish sometime this year that I think should help clarify some of our ideas about the methods for this.

Claire Butler, PhD: Thanks so much. And just one follow-up question. Do you see the lung deposition modelling validation being more instrumental in terms of being non-Q1, Q2 the same, or would it be kind of a universal expectation depending on whether it's just for virtual trials versus justifying non-Q1, Q2 same as?

Ross Walenga, PhD: I think in that area, our thinking is still evolving. I think it would certainly be a useful tool. I think PBPK also could be useful. It may sort of depend on what aspect you're thinking of, but I think it's always going to be helpful. Just hard to say how important it is at this time. Thank you.

Claire Butler, PhD: Thank you

Giuseppe Randazzo, MS: Thank you, Claire. Thank you, Ross. All right, again, in the interest of time, we should probably move on to the third one, please.

Virtual Presentation by Maitri Sanghavi, MS

Hello, I am Maitri, the research scientist at Certara MIDD Division. I am here to make one important point: that for certain generic drug products, simple PBPK models are not always enough to support a bio waiver. Common practice in BE analysis is to use compartmental absorption model or direct in vitro dissolution input. If predicted C max and AUC fall inside 0.8 to 1.25, the model is treated as good enough. And mechanistic PBPK is often set aside, and it's believed that it's too complex or too slow or too expensive.

What I want to put forward here is that complex products may need something more, models sensitive to in vivo physiology. For example, surface pH buffer capacity, particle size, regional permeability should be modeled explicitly. And virtual BE that captures the between subject variability and within subject variability. And this is what permits extrapolation of formulation, populations, and prandial state.

So, these are certain scenarios where simpler model can mislead. First, modified release and complex formulations, and 2nd is complex food effects, where we have to consider buffer capacity, gastric emptying, bile salt micellization, etc. And only mechanistic models can reproduce them. Then we have a special population predictions where a single empirical Ka cannot extrapolate.

Let me make this concrete. This is the case study of bempedoic acid. This is BCS class 2 weakly diprotic acid. And it is having very low solubility at pH below 6. High passive permeability, so absorption is dissolution rate limited. One 180 mg IR tablet is developed for the adult and pediatric oral suspension was under the development. Using the, so this modelling was done in Simcyp V24, using the simple model where bulk pH was considered as a surface pH for 180 mg fasted, the model over predicted the Cmax by 44% and Tmax by half. And, but you can see that percent prediction error is also outside the acceptance limit, though it's fine for the AUC, but Tmax and Cmax tells a different story.

The fix is mechanistic, as the Noyes-Whitney equation on the screen shows dissolution rate depends on the surface solubility and the term changes with the local environment. As the weak acid deprotonates, the particle surface local pH drops below the bulk pH, which lowers the solubility and slow down the dissolution. And surface pH model recalculates the particle surface pH at every time point. And you can see that T max moves to 2.7 hours and percent prediction error improves. Now all three parameters sits inside the 0.80 to 1.25 acceptance criteria.

So same compound, same clinical data, just mechanistic modeling provides better insight. This model was validated across the single dose, multiple dose, fasted, fed, and ethnic population. We then virtual bioequivalence trial between pediatric oral suspension and reference IR tablet. And across all 10 replicates, the 90% CI for Cmax and AUC fell between 84 to 99%. and this is the evidence for the pediatric suspension. Avoiding a clinical BE study in a population that is hard to recruit, costly, and ethnically sensitive.

In closing, three recommendations to sponsors don't stop at compartmental and direct solution input or post-hoc WSV in your model when mechanism matters, invest in mechanistic models early. To reviewers, Cmax and AUC inside 0.8 to 1.25 is necessary, but not sufficient. Tmax shape and underlying physiology matter for extrapolation and to provide explicit predictable guidance on acceptable acceptance of VBE supported by mechanistic PBPK as a guidance for generic complex products. So simple models can keep us inside the acceptance limit, but mechanistic models can provide valuable insights, and that is what can unlock biowaivers for certain drug products. Thank you, everyone.

Giuseppe Randazzo, MS: Thank you very much. Now we are running out of time. We have a few more. So any quick comments, any thoughts? Because if not, why don't we just move right on to the next one, please? Next presentation.

Virtual Presentation by Sivacharan Kollipara, PhD

Hello, everyone. Good afternoon, good evening, and good morning. I'm Sivacharan from the Biopharmaceutics Department of Dr. Reddy's Laboratories. Today, I would like to talk about model-integrated bioequivalence in generic research, case examples, and future research. A standard disclaimer: the opinions present in this particular presentation are mine, and they do not represent that of Dr. Reddy's Laboratories Limited.

The short outline for this presentation is introduction to MIBE in generic research, then I will talk about two case examples, and then I'll conclude with future scope for research in the MIBE applications.

So, what exactly is MIBE? Model Integrated Bioequivalence is basically a regulatory approach where one can use modeling and simulations in the place of the traditional clinical trials, which can act as a pivotal evidence for the submission that demonstrate the bioequivalence between generic product and the reference product. Typically, in terms of conventional BE, few cases will result in burden for the industry, and some of those cases would be using the larger number of subjects in the study, longer duration of study, and for the drug products exhibiting high variability. In those cases, model integrated bioequivalence approaches that integrates formulation, drug, physiological aspects together with the clinical PK data can act as a pivotal evidence to demonstrate that generic drug product is bioequivalent to the reference product.

This slide talks about the use of population PK models in model integrated bioequivalence approach. And this is the typical overview of the workflow of the population simulations that can be used to support the bioequivalence between reference and generic products. Although it is not very common practice for the generic industry, to use population PK, but the use of population PK to demonstrate bioequivalence between reference and test product is increasing in the recent past few years, because it has a lot of applications in the long-acting injectables and oral dosage forms, and also in the specific cases where it is not feasible to develop and validate a physiological model, for example, in those cases where there is no biopredictive resolution available.

With this introduction, I would like to talk about two case examples. The first case example talks about MIBE to wave off a repeat pivotal study for clopidogrel tablets, 300 milligrams. The challenge in this case is that the pivotal study had a sampling up to 12 hours, and thus it poses some questions on the estimation of AUC infinity. And the assessment, so to address this particular regulatory query, we have constructed a population PK model using the MIBE approach, and it has been validated in the fasting and fed conditions. As a part of validation, type one error has been assessed in fasting and fed conditions, and it is found to be less than 5%. The validated model was used to extrapolate the bioequivalence study results of the pivotal study up to 10 half-lives, and the simulations have indicated bioequivalence between the test and reference product with the extended sampling, and it is also assessed that sampling up to 12 hours in the pivotal bioequivalence study did not compromise on the bioequivalence. So, this has resulted in a lot of reduction in the time, and it enabled cost savings.

The next case example, which is hypothetical, and it talks about the extrapolation of the sparse data to full profiles. Typically for the drug products such as long-acting injectables that exhibits a drug release over a longer period of time, rich PK sampling is required to completely characterize the PK profile. But this poses a lot of challenges in terms of high

cost and also induces operational complexity. In this case, MIBE can be used, wherein we can do only a sparse sampling and using a validated model, full PK profiles can be constructed. Here, we present a hypothetical example wherein the sparse sampling-related BE assessment, when it is compared with the simulated full PK profiles, the prediction errors are less than 5%, and thereby validating the use of MIBE in the specific applications. So, the benefit in this case would be it will enable the significant reduction in the study duration cost. And most importantly, it reduces the patient burden as well.

So the conclusions based on the assessment and the case studies is that MIBE approaches will result in significant value to the generic product development and it has a lot of applications as we have witnessed. Early engagement with the agency through MIBE pilot program or the pre-development meeting can definitely facilitate successful implementation of MIBE.

The future research areas in this particular MIBE applications would be providing A validation framework for MIBE models. For example, a specific guidance that talks about type 1 error estimation and uncertainty would be very helpful. A standardized framework for specific applications in terms of guidances would also be very helpful. Although the population PK models reported in the literature have been used for long-acting injectables, they can have a lot of applications in oral formulations, inhalation, nasal formulations, and topicals, and some research in this direction will be very useful. Wherever it is applicable, the PSGs can be included to use the MIBE as an alternative bioequivalence option. And submission related documentation templates, such as model analysis plan and reports. The templates for these two aspects will be very much helpful for our industry to understand how the submission package can look like. Most importantly, publishing the scientific articles, knowledge sharing, and the training for enhancement of generic industry capability can also definitely increase the use of MIBE in generic research.

With this, I would like to thank Dr. Anuj, Dr. Rajkumar, Dr. Chandra Teja for their support in making this presentation. I would like to thank the CFTs and Dr. Reddy's management for providing all the infrastructure and the support. Last but not the least, I would like to thank the US FDA and the FY26 GDUFA Public Workshop Committee for providing me this opportunity to express my thoughts on model integrated bioequivalence. Thank you.

Giuseppe Randazzo, MS: Thank you. And there are some specific research ideas there on that second to last slide. So any general thoughts there? All right, so we've captured a lot of that. There's one or two more, Sam, there's one in person. Is there one more presentation or is the in-person one? OK, just one more in the next session, two more. OK, please, again, yeah, thank you.

Virtual Presentation by Amy Lukau, PhD

Good morning, good afternoon. My name is Amy Lukau, and thank you to the GDUFA Workshop Committee for the opportunity to provide this public comment. My remarks focus on generic autoinjectors and intranasal rescue devices intended for emergency use and on where additional regulatory science may be needed to support the development and assessment of these products under real-world use conditions.

Emergency use products present a distinct human factors challenge because they are not typically used under calm or controlled conditions. They are often used under time pressure where rapid administration is expected, and there may be little opportunity to recover from an error once a sequence is initiated. They are also used under stress and cognitive burden. In an emergency, users may be operating under panic, urgency, or reduced working memory, which affects how they perceive device cues, instructions, and complete critical steps. Additionally, the environment itself may be variable. These products may be used in noise, poor lighting, with gloves, in adverse weather, or under physical movement and distraction. And finally, the user population is broad. Depending on the context, the user may be a layperson, a first responder, a caregiver, or a military user. That diversity increases the importance of intuitive design and clear task execution.

For emergency use generic combination products, equivalence should not be understood only as a matter of whether the product performs the intended mechanical action. Functional equivalence is clearly essential, but in emergency use settings, additional dimensions may also determine whether the product can be used safely and effectively. Perceptual equivalence refers to whether users recognize and interpret the product in the way they expect, including cues related to orientation, activation, and feedback. Cognitive equivalence refers to whether the product supports the same understanding, decision making, and use sequence under stress, especially when the user has limited time and reduced cognitive bandwidth. And these issues come together in critical task alignment. The central question is whether the essential tasks required for safe and effective use are recognized and completed in the same way relative to the reference product.

This is why interface and sequence differences deserve careful attention in emergency use products. Differences that may appear modest during development may not remain modest in practice. Under emergency conditions, even subtle differences in interface, cues, or sequence may alter user behavior. That may result in delayed administration, especially when users hesitate or need additional time to interpret what they are seeing. It may result in incorrect operation, if device orientation, activation, or sequencing is not

understood as expected. For an autoinjector, a seemingly small difference in grip, orientation cue, activation force, or feedback mechanism may change how quickly and confidently a user recognizes and completes the intended steps under stress. For an intranasal rescue device, differences in positioning, handling, or multi-step sequence may affect whether the user delivers the product correctly on the first attempt or becomes uncertain about redosing. In both cases, these differences may also create use confusion relative to the reference listed drug. And in emergency use settings, those outcomes may become clinically meaningful use-related risks, especially when timely and correct administration is central to the intended intervention.

For these reasons, I believe additional regulatory science may be valuable in several areas. First, there is a need for a better definition of emergency use equivalence expectations. Second, greater clarity may be helpful around bridging approaches for interface differences, especially where core function may appear comparable, but user perception or cognitive processing may differ in meaningful ways. Third, stronger critical task comparison methods may be useful to help establish whether the essential tasks remained aligned across products and use contexts. Fourth, a more explicit human factors expectations for ANDAs could help reduce uncertainty for both developers and reviewers in this space.

One potential path forward is what I refer to as comparative equivalence modeling, or CEM. CEM emphasizes task convergence, cognitive equivalence, perceptual cue similarity, and risk alignment as structured dimensions for reasoning about equivalence in emergency use settings. My closing point is this. Emergency use devices must behave predictably, even when people do not. For emergency use products, what matters is risk alignment, not procedural mimicry. This is why a more meaningful future for comparative human factors may depend not only on comparative testing, but also on comparative reasoning, grounded in cognitive equivalence, perceptual convergence, risk alignment, and environment-specific user burden. Thank you again for the opportunity to contribute these comments.

Giuseppe Randazzo, MS: Thank you very much. And task studies we've heard a lot about recently, so, and I know I have from my members. Any general thoughts or comments there? We have one, Brandon.

Brandon Wood, MS: Yeah, no, I would just say, you know, I think it's a good framework that Amy had laid out there. Obviously, there's a lot of work in this space right now, and, you know, I wouldn't necessarily limit it to considerations with respect to emergency use products. I think, you know, now more than ever, there are more and more complex drug device combination products being approved. you know, like electronic user interface is top of mind for me and how that is, you know, not necessarily fully compatible with the

current systems, but maybe to, you know, continue to consider this framework, not just within the scope of injectors, but, you know, the next, you know, five, 10 year outlook of complex drug device combination products. I think that would be very important. So,

Giuseppe Randazzo, MS: thank you.

Robert Lionberger, PhD: For the industry perspective, are you sure what an emergency use product is?

Giuseppe Randazzo, MS: Well, I think with Brandon's comment, I'm not sure it matters, right? So he said, yeah, that's one way to look at it, but also he wanted to go potentially beyond that. But go ahead, if anyone wants to answer.

Robert Lionberger, PhD: The question is, do you think FDA is clear on what people think an emergency product is?

Giuseppe Randazzo, MS: Oh, gotcha.

Brandon Wood, MS: I think some are quite obvious, but others, you know, to your point, some products that are used in, you know, acute situations, I think there's a bit of lack of clarity in terms of whether or not the full emergency use expectations would be applicable. So I think, you know, emergency use. Some are clearer than others, but I think there's also a bit of a gray area there in terms of, you know, what levels of acute use might be applicable to a certain device combination product.

Giuseppe Randazzo, MS: Thank you both. All right, next presentation.

Virtual Presentation by Irene Rossi, PhD

Good morning, good afternoon, and good evening everyone. I'm Irene Rossi and I would like to briefly introduce you to the topic, Applied Solutions to overcome the challenges associated with the spray dry powders in the generic orally inhaled and nasal product development.

Dry powder inhalers are very complex products where like different elements, so the type of the API excipients and the formulation, so all these two comes together. And as well like the device, so if it's a prototype or where it's moulded, the primary packaging container, blister, capsule, so and as well like the manufacturing process, so powder feeding and powder dosing are all influencing the final performance. Especially from an aerodynamic properties perspective.

So, traditionally, dry powder inhalers are mainly based on a carrier-based formulation, so made of about usually only three different components: drug, lactose, so and force control agent like magnesium stearate. However, when it comes to engineered powder, so there are much more different technologies that are explored, have been used, and also used on the product approved on the market. And of course, spray drying is the main technique and the most versatile one. So that allows to create very specific and defined type of particles.

These powders are much more complex and they have a completely different physical chemical characteristics, as you see in the slides. So starting from the particle size to the morphology and shape of the particles, density of the particles, that is very low compared to carrier base, are more prone to electrostatic charge. but on the other side, so they don't incur into powder segregation. So all of these different elements, so needs to be considered and are impacting, so especially the feeding and filling process. All different approved engineered dry powder inhalers on the markets are filled by drum filling, so regarding of the particle engineering technology used, and as well like the type of primary packaging container.

And I would like now to show you very briefly an example of how this micronized engineered powder with a much more homogeneous PSD, so are also impacting us, especially powder feeding. So inline sieving is usually used when it comes to spray dry powder, so to have a better flowability of the powder inside of the device and so therefore dosing inside whatever is the packaging container, so capsule or any different type of device. And in this study, we took budesonide as like a model drug that we mixed with lactose to have a very homogeneous particle size distribution, so all in a very small micron range, or we made like a very common carrier-based blend, so mixing budesonide with the Respitose, SV003.

Inline sieving was used for both powders and different fill weight, so was achieved for the two powders, so due to the different density, so of the two formulations. But however, a very good RSD was achievable, so using drum dosing and inline sieving. However, a segregation effect was observed for carrier-based powder, so inline sieving would not be a good tool for carrier-based powder, but it is a tool usually used, for example, more with engineered powders.

So in conclusion, engineered particles, especially spray dried, are usually much complex metrics, so then carrier based. So where the role of excipients and as well like of the spray dried feedstock solution, so really needs to be understood and controlled and will impact properties such as dissolution and release. The particle engineering process is tailored to obtain specific and defined particles characteristics, so it becomes more challenging then to develop, of course, generic formulations. And the type of process that is used needs to be tailored to the final product characteristics, so drug chemical properties, indication, and

also dose requirements. In vitro techniques to analyze properties such as particle morphology, density, and water content, so become fundamental for engineered spray-dry powders. Powder filling and feeding processes are more critical, so for these type of powders that are actually more challenging to fill. and some processes that are applied to carrier base that cannot be applied to particle engineered powders and vice versa. Therefore, characterization, understanding and control of spray drying, feedstock composition, particles, spray drying and powder dosing processes are key for the development of products bioequivalent to original engineered DPIs. Thank you for the opportunity to briefly present this topic and some proposed future areas of research. So here are my contact details, so if there is any question.

Giuseppe Randazzo, MS: Thank you, Irene. In the interest of time, one or two comments, and if not, we'll move on. She was pretty explicit about some ideas, so you have them there, Sam. All right, I think there's one more virtual, and I think there's one.

Virtual Presentation by Laleh Golshahi, PhD

My name is Laleh Golshahi. I'm an associate professor of mechanical engineering at Virginia Commonwealth University and founder and CEO of 3D-Inhale, translating research and nasal drug delivery into tools for drug product development. My talk today is titled Human Relevant New Approach Methodologies for Nasal Drug Delivery to the CNS.

Interest in nose-to-brain delivery has grown substantially since it offers a non-invasive pathway to bypass the blood-brain barrier for CNS therapeutics. But that growing interest isn't yet matched by validated human-relevant models that regulators and developers can rely on to predict nasal drug absorption and distribution to the brain. That's the gap I'm addressing today and why establishing NAMs is specifically for nose-to-brain delivery should be a GDUFA priority.

Three reasons why NAMs are urgent here. First, the brain is a protected compartment. The blood-brain barrier blocks the vast majority of therapeutic candidates. Small molecules that do cross require systemic doses high enough to drive peripheral side effects. Second, the margin for error in CNS drug development is uniquely narrow. Off-target effects on mood, cognition, and behavior make safety missteps especially consequential. Third, animal models lack predictive validity for human nose-to-brain delivery. Preclinical success routinely fails to translate. In stroke therapeutics alone, only one in 500 candidate molecules reached approval. Human-relevant NAMs are positioned to close this translation gap.

The current FDA nasal guidance dates to 2002-2003, nose to brain delivery for CNS pathologies was not a primary consideration back then, and that gap is showing now. Two structural problems are device performance is characterized without nasal context. All patients are essentially treated as anatomically identical. Second, there is growing use of single geometry models, but with no standardized image quality standards, no conversion protocols, no anatomical landmarks, no specialist verification, and no concurrent guidance on device positioning, meaning administration remains uncontrolled. For a delivery route where drug molecules cannot reach the brain via systemic circulation, These are foundational gaps that limit predictivity and leave developers without reliable scientific basis for regulatory decision making.

Inter- and intra-subject variability directly impact regional nasal deposition. Our data make this clear, even with identical products, regional deposition varies substantially across geometries. Given how small the target region is, meaning the olfactory epithelium, which is only a fraction of nasal surface, variability in delivery to that specific region is even more substantial. No single geometry is representative. Plume angle and spray characteristics alone cannot predict targeted delivery. This has a direct regulatory implication. Bioequivalence frameworks for nasal CNS products need to be population-based and anatomy-informed, not built on a single model.

Anatomically detailed nasal models address three gaps, realistic use conditions where device positioning is precisely controlled, population relevance where variability across age, disease, and anatomy is captured, and improved endpoints due to direct regional deposition measurement. But translating this into a nose-to-brain NAM requires solving a real challenge. Olfactory epithelium and superior turbinate are anatomically adjacent. Defining the olfactory region with the precision and reproducibility A regulatory model demands requires establishing A standardized, specialist verified boundaries. Administration angles, insertion depth, and anatomy shift drug delivery toward or away from the olfactory epithelium. These interactions cannot be predicted from device characterization alone. Optimizing device and formulation parameters against anatomically representative nasal models provides a mechanistic path to bioequivalence demonstration grounded in human-relevant NAM platform. For drug product developers, that's actionable guidance. For regulatory scientists, it's scientific foundation for decision making.

Three interconnected research priorities are suggested. First, enable predictive early-stage assessment of nasal drug products designed for olfactory targeting by supporting human-relevant NAMs. Second, apply NAMs to characterize the range of various drug modality delivery at the nasal epithelium across different populations, enabling drug product design

that accounts for dose variability. Third, extend NAMs to predict permeation across the olfactory epithelium, providing A mechanistic foundation for regulatory guidance on growing nose-to-brain drug delivery products. These 3 priorities form a coherent research program. closing the gap between scientific innovation and regulatory capability. Thank you for the opportunity to share these thoughts, an area I believe is critical to advancing safe and effective nose-to-brain drug delivery. I look forward to working together on closing this regulatory science gap.

Giuseppe Randazzo, MS: Again, very explicit ideas for the FDA. I think it's the in-person. So I think we can get started with the in-person presentation. And we have Peng from USP. Thank you, kindly introduce yourself, sir.

Virtual Presentation by Peng Zhang, PhD

Thank you, Giuseppe. Good afternoon, everyone. My name is Peng Zhang. I'm a principal scientist at the excipient group at USP. First, I really want to thank the organizer for this excellent opportunity. The focus of my presentation today is on PLG polymer nomenclature. And the quality test methods.

What are PLG polymers? They refer to lactide, glycolide, and lactic acid, glycolic acid polymers. They are biodegradable polyesters, widely used in controlled release formulations. I really want to emphasize both PLGs and PLGAs here. they represent two different synthetic routes, ring openings for PLGs and polycondensation for PLGAs. They have different compositions, which impacts the drug performance.

Why using PLG polymers? There are so many benefits. I want to highlight several today. Biocompatible, biodegradable, very low toxic effects and the tunable. So far, there's around twenty-eight FDA-approved branded drugs and six generic drugs in this area.

There's many challenges in this area regarding PLG polymers and PLG polymer-based drugs. I want to highlight several from a PLG polymer raw material perspective. First, naming. On the market, the names are not consistent. In many cases, they are even wrong. Variability, batch to batch, manufacturer to manufacturer, due to lack of standardized methods and reference materials. Thirdly, not all the products are eligible for compendial development.

To solve all these challenges, USP is establishing a comprehensive framework, offering both compendial standards and also emerging solutions. To address the naming challenge, we published a stimuli article proposing a naming system. Later, FDA adopted this system by updating 16 PLG polymer entries in their system. We truly appreciate the collaboration. I

want to take the first one as an example. You know, the updated one I show in purple color here. Our naming system specify monomers, monomer ratio, molecule weight, and end group. You can see from the previous name, first, the monomers are wrong, or this is a ring opening polymer, ring opening polymer. Secondly, the end group is missing.

To addressing the variability challenge, we have been advancing and standardizing characterization methods for PLG polymers. This slide highlights our efforts in the general chapter area. The table here summarizes our portfolio. For the test method for PLG polymers, I want to share that our chapters are focused on 2 technologies, NMR and also GPC. The methods are for molecule weight, polydispersity, monomer ratio, and block length determinations. Happy to share with you for the first two. They are currently official. In addition, we published a general article on the GPC-MALS, absolute method for PLG polymers. We are developing a technical note based on this article.

Here's our comprehensive framework for LG polymers. Of course, you know monograph. We published 7 monographs already. The first four are currently official. Reference standards, stimuli articles, general chapters. In addition, we have been developing analytical reference materials, case study, peer review articles, education course, and more. Here's our LG Polymer web page. Almost all the content I covered today are available from this web page.

Stakeholder engagement and collaborations are very key for USP. Here's our contact information. First, this is a public comment presentation. I want to take this opportunity to recommend strengthening collaboration between FDA and the USP in the area of improvement of character of characterization, sorry, characterization tools for polymeric excipients to support the compositional sameness evaluation. From the GDUFA research perspective, really want to... We hope you know USP will have more opportunities in the future in collaborating with FDA in advancing and also standardizing the characterization methods for complex excipients, not just LG polymers beyond LG polymers, other complex excipients. That's all. Thank you for your attention today. Thank you.

Giuseppe Randazzo, MS: Hey, if you don't mind, so we have a unique opportunity here today, since he's here in person, attending in person. Are there any questions? OK, Jim, thank you.

James Polli, PhD: Something that came up, I think, this morning about functionality of excipients. I think people really think about that very, very frequently. I'm kind of under the impression that USP often doesn't get involved in that, at least historically, at least maybe in the context of maybe just this polymer. I mean, do you see a role of functionality testing for at least this polymer or other polymers?

Peng Zhang, PhD: Yeah, a very good question. First, I want to clarify, we are addressing excipient performance through our general chapter. That is our general chapter 1059, excipient performance. So we are taking a different approach from EP. Definitely, you know, functionality, performance-related properties are very important for excipient. For LG polymers, of course, yeah. Definitely, you know, we are working on the test methods for... Molecule weight, polydispersity, block length; they are both quality critical quality attributes and also performance attributes, so definitely there's other properties, like you know, glass transition temperature and viscosity. We definitely, you know, thinking other approaches to introduce test methods for performance-related properties. Definitely, yeah, just wanted to share that information, yeah.

Giuseppe Randazzo, MS: Any other questions? All right, let's give Peng one more round of applause. Thank you, sir.

Peng Zhang, PhD: Thank you. Thank you.

Panel Discussion

Giuseppe Randazzo, MS: All right, for the second half of the session, and we ran a little over in the first half, but for the second half of the session, we're going to get into a little bit of, again, how do we work, how does industry and other stakeholders work with the FDA regarding the regulatory science research program? Before we begin, I do want to give an opportunity to have Dr. Victoria Keck, excuse me, and Xiaoming introduce themselves.

Victoria Keck, VMD: Hi, everyone. I'm Vicki Keck. I am currently the Acting Associate Director of Generic Stakeholder and Global Engagement. And my background is, you'll see it says VMD. I am a veterinarian with comparative medicine and toxicology experience. I've been with OGD since 2015.

Xiaoming Xu, PhD: My name is Xiaoming Xu. I'm a division director in the Office of Pharmaceutical Quality Research. So I lead a researcher, a group of researchers conducting research, and a lot of research are in the generic space. So thank you.

Giuseppe Randazzo, MS: Thank you very much. So to the audience, in preparation of this session, we worked with the FDA, the colleagues here across the panel, with the FDA and talking about, again, how to operationalize this, how to take the next step as far as we have this meeting once a year, we have good conversations back and forth and maybe some industry challenges, regulatory impact and research that may be needed. We want to talk about, again, the next phase of that. How does industry get more involved if it's reasonable regarding the research research projects, and with that, two individuals who are kind

enough to put together an infographic, I think it can really set the stage for the conversation, Sam.

Sam Raney, PhD: Thank you, Giuseppe, and thanks to the entire panel who actually helped to prepare this. So over the last decade of GDUFA and the GDUFA research program, the generic drug research program has evolved into quite a powerful engine for being able to build scientific bridges across the knowledge gaps that we identify each year in this meeting, in this annual GDUFA public workshop. And those scientific bridges are operationalized through new tools, new bioequivalence approaches. It's been a real success story for being able to lead to approved generics for complex products that were practically impossible to develop before GDUFA, and this is a fully functional engine, kind of depicted here in this illustration in the middle, and it's evolved to be quite sophisticated to have all the pieces that, after this workshop, as we will then go into defining the FY27 GDUFA research priorities, that this engine then drives those priorities forward all the way till we get final approval of products for patients.

And one of the things we'd like to do, as we've done each year to kind of evolved this process and made the engine more powerful, is to understand this year where we can enhance it beyond what we would ordinarily do with this meeting, where this meeting ordinarily would lead to the FY27 GDUFA research priorities being defined. And then from that point forward in the past, it would have been up to FDA to really drive this engine forward. So while this workshop is in many ways the ignition switch for the entire engine that drives the process to address the scientific challenges we're discussing. What we'd really like to explore in this session is how industry expertise can continue to be involved and sort of be a force multiplier, as Brandon Wood has described it, at multiple entry points within this process, where if there's no industry engagement, it is still a fully functional engine, but in every instance where industry can engage, there might be an opportunity to make the Engine function even more powerfully, and one area is an increased level of advice in the early stages, so we're going to explore how could generic industry expertise help, for example, in several areas where, after the GDUFA research priorities have been defined to one, inform the design of the specific research projects in such a way that it really optimizes the outcomes to be purpose-built for the way that industry would operationalize them and for the way that FDA would utilize them. And this, for example, might inform the way that a funding opportunity announcement might be announced for a grant.

And then the next part is, once those grant announcements go out and numerous proposals come in, as an example, could industry experts assist with the review and selection of suitable research proposals in much the same way as we've seen several

proposals in the public comments here, and it's been incredibly valuable to have the industry's perspective and the industry expertise to say, you know what, these ones really resonate with them, with us as industry, and would be right on point for exactly the type of thing we need. Whereas another aspect might be, well, this is very interesting research, but it's a little bit academic in nature.

And 3, once those research projects are awarded, once the research is underway. Could industry experts provide technical guidance on the conduct of research activities throughout their research? You saw during this session how Claire was very interested in some research that had already been prioritized relating to inhalation modeling within the lung. And Ross came up and spoke a little bit to what was going on with that. And I think that may reflect something we heard even in preparation for this session, that after the GDUFA research priorities are identified, and they're essentially the marching orders for FDA to drive this engine forward, that industry may not feel as connected to the progress of that research as they might ideally like. And so the question is here, could they continue to advise during the process and provide technical guidance even as the research is ongoing?

And these would all be advisory roles, but there may be even a further level of engagement that involves collaboration to actually be able to support ongoing research studies at, let's say, University of X, by supporting them with test materials or study samples, or even going further to say that sites within industry could collaborate on the actual conduct of multi-site research activities, so that research might be driven by a particular award recipient, but that this collaboration at sites within industry on that. For example, as seen in point 6 there, would it be possible to facilitate rapid cycles of research, adoption, refinement, and really to be able to accelerate kind of each of these wheels of progress within the engine?

And then ultimately, as insights, scientific insights are gleaned from the research that moves forward, then comes the question of, well, how do we interpret the science? How do we translate this into best practices that are practical? And this is also an area where industry may be able to help us apply by 7, optimizing practical ways to implement the scientific insights, or even guiding where PSG revisions might need clarity or flexibility. Because these PSGs basically describe the recommendations then that operationalize those scientific insights, even moving forward to saying, could we have industry suggest technical content that enhances the utility of these PSGs, perhaps including BCS classifications, or if the research has shown that there are a known set of specific impurities for a particular drug product, to actually call those impurities out within the PSGs, say, these are the impurities of concern, and perhaps these are the thresholds that we would want to target for these particular impurities because the research suggests that these would be acceptable thresholds.

And even going further to the last point there, can industry experts help to identify specific products to prioritize for PSG developments that would not ordinarily be prioritized under our other GDUFA commitments? Of course, developing PSG recommendations for those products would again need another cycle of research, and this leads us right through into the process again.

So, what we'd like to do for the rest of the session is to explore how each of these potential areas where industry expertise can come into the process and serve as a force multiplier. I know it might be feasible, might be operationalized, and what it would take potentially through interaction through the CRCG for research activities, for expertise to come together from industry and FDA and academia to be able to ride this process forward and make it even better.

Giuseppe Randazzo, MS: Thank you very much, Sam. I know Ahmed, thank you too for the help with the infographic. Very well done. So as we get into this, for the next 20 to 30 minutes, we'll talk about how we can think about the advise, collaborate, apply. And the idea is, you know, how should industry engage in GDUFA research? So what I'll do is I'll make the first question somewhat general and just to open up of course, to all panelists. You know, how can we structure FDA and industry engagement so that GDUFA funded research translates into practical, implementable recommendations while preserving FDA's independent regulatory authority? I'll open it up to anyone.

Brandon Wood, MS: Yeah, no, this is Brandon. Happy to kick things off here. So I love the infographic. I think this is perfect. And thanks, Sam, for keeping the force multiplier. I really do believe that here. I think, you know, really in terms of an industry perspective, there's, you know, design, there's execution, and there's interpretation. I think they're all, you know, incredibly meaningful inflection points in these research activities. In terms of design and execution, the reality is that if you have industry engagement, we can make sure that we're asking the right question, that, you know, there's great focus on the actual problem that needs to be solved and, you know, hopefully coming to a solution that can be implemented in a practical manner. I think that's incredibly important. Execution also, you know, industry has a lot of experience in some of these areas. So if we have an ability to help you avoid some real life failure modes that we've already experienced, I think there's a lot of value there in helping to ensure there's efficiency. and effectiveness in the work that's being done. And then probably, you know, the last, again, in interpretation or application as it is in the infographic, you know, at times, certain studies can, I think, reflect a narrow set of controlled conditions, right? So then extrapolating that out and having that, you know, apply to entire product classes or product types, industry may have information that helps see some of those results maybe in a different scope, in a different light, or allow the

interpretation of those studies to be conducted. And, you know, again, a manner that's going to be most efficient in completing and ensuring, you know, I think, quick and proper development of these complex products, but just a few thoughts from my end.

Giuseppe Randazzo, MS: Thank you, Brandon. Any other thoughts?

Victoria Keck, VMD: So from the, this is Vicki, from the stakeholder and global engagement perspective, there are three things that I think about. First and foremost is impartiality. So I think it's important that in this engagement that we have structured level field of access. And I think the CRCG would be a great intermediary of getting input from industry and weighing it by technical merit, right? So they can intake information, share it with FDA. We can take it under consideration. The second piece then is transparency, sharing where we are with research. As Claire had, you know, she kind of showed that she mentioned that last year we were working on a particular research and she wanted to hear where that was. She learned in this meeting, but we could work with CRCG to have a mechanism by which we can update industry with where we are on our research, whether it's translating into a product specific guidance or not. And then third is responsiveness. This mechanism that we will hopefully work on will help us keep pace with science.

Xiaoming Xu, PhD: This is Xiaoming. So I do, you know, second both Brandon and Vicky said, and also I like this infographics a lot in terms of connecting, I think, many moving parts, many partners, you know, industry, FDA. We're all working together on solving some challenging problems. And so I look at this and actually I want to kind of express in my own thinking how, you know, how I fit this into, you know, how I approach using the example of problem solving. So how does this fit together in terms of working together, solving problems? So, I want to express there are, in my opinion, 5 stages of... solving a problem, starting with recognizing we have a problem. I think we have been doing a pretty good job, you know, with workshops like this, open dialogues, feedbacks. We're pretty good at recognizing we have some challenges, some problems. And the second stage, I would argue, is actually the area that we are not doing so well, which is understanding the problem. This involves us asking difficult questions to getting deeper and deeper about what it is that's preventing us, let's say, come up with a guidance or preventing the companies from actually follow the guidance or preventing the methodology from being utilized in support of an application decision. So I think that what exactly is the problem I see oftentimes we skip that step or we very quickly jumping over the step. And then the third stage, which is, of course, we talk a lot about research, which is spending time actually come up with the solutions to solving the problem. And then once we have a research outcome, a finding and understanding, of course, we have to communicate. And this will be through either publication from FDA or FDA sponsored academia partners with

public publish the results or through the guidances, communicate to the industry. And the last step, I would say, is industry actually implement or actually put those into action where the rubber meets the road, where the actually the solutions being tested. So I see we along this 10 interactions, I see the industry has a tremendous value in stage one, stage two, and stage five, where you help us defining the problem, help us understanding what's the problem, and help us to implement, maybe also providing feedback to us what doesn't work well. And also, I think the other way is what has worked well that reinforced that cycle of iteration of continue to work on to finding solutions. I see quite a few of this that either through advice or through collaboration. I see industry has a particular value that can contribute towards that problem identification, again, understanding problem. I see oftentimes it's you don't come forward clear enough about what exactly you are struggling, that we are not actually finding the right solution to the right problem. So let me stop here. But I do like this process, how we are working together, and I do agree, CRCG can play a critical role in that interface, helping us making more bridges.

Giuseppe Randazzo, MS: It's very good, Ahmed?

Ahmed Zidan, PhD: I believe this is a very good opportunity to highlight the importance of the GDUFA research, not only in shaping the regulatory sciences that we are doing and supporting the development of the guidance, but from the other side also, it provides some actionable outcomes where industry can use to produce their products. So the framework here is, I have, I can say, more ambitious vision about the framework here where we can move from more scattered basis of collaboration with the industry into research to implementation framework where we can structure the engagement of industry with the FDA at different stages, as Sam just mentioned. And of course, CRCG can be the platform to handle this. However, We need to identify or define the role of each part here. So CRCG is very important to have the governance rule where it coordinate all the interaction between the FDA and the industry. However, still, it should keep the independence opinion of FDA on developing guidance and in recommendation and in barrier utilization. However, as Xiaoming mentioned, getting the feedback from industry on barrier utilization of product-specific guidance, not only by requests that's submitted to agency, but it should be based on systematic studies and needs in the market and how many, for example, firms or applicants are affected by this PSGs and the market share for the product, for example, and the need and also number of patients that's affected by developing this PSG and how to reduce the time for the market. And we have seen in GLP1, for example, it was a very nice example of some of the new products that's newly generated or approved. And we internally have a policy, or not a policy, a procedure in FDA, like to prioritize PSG development for newly approved drugs. but the industry needs an input. I think it is very, very integral in this polarization in determining the contents of the PSG, how it can be

helpful. And even like sharing with FDA opinion about the level of flexibility and prescriptiveness in the PSG, how we can use this collaboration between FDA and the industry through the CRCG in determining the level of specificity in the PSG, where science is already matured and we can rely on the already available science to set up exact specification and prescriptions in the PSG, or we can have it as flexible as long as there is some evolution in the science and some like different ways to like establish the endpoint as it is needed. So, I believe it is very, very powerful tool here, and if we use it, we can we can have like a very good framework.

Giuseppe Randazzo, MS: That's helpful. Thank you. I see Claire is in the audience.

Claire Butler, PhD: Sorry, just one more comment for myself. Just with respect to PDEV meetings, just to highlight that, you know, these are invaluable and fruitful tools for us, you know, as you know, from industry. At the moment, the recommendations are to have, say, one PDEV meeting annually, and you know, I think this indirectly addresses a comment from the last session where FDA may see a lot of changes in ANDA submissions, you know, whereas let's say the specific approach would be quite different to what was discussed in the PDEV. And I think that's because scientific thinking changes and can change quite dramatically in a year time. So I suppose my comment would be if there was avenues where we could, you know, introduce more flexibility about you know, how many PDEVs we might have in a year based on this scientific advancement. That would be really helpful for us because PDEVs are just, they're invaluable. You know, they really are.

Giuseppe Randazzo, MS: That's helpful. Thank you.

Uwe Niesner, PhD: Yeah, thanks. I would like to add to that. First of all, I can recommend to all to go to PDEVs because it's very valuable advice and you see the flexibility if you come with very good product-specific data. I would echo that as well. We have a bit of a gap, I would say. The PDEV meetings are particular, they are probably quite a lot of work for FDA, but as well for the applicants. They have a four month cycle. And then we have the pre-ANDA meetings, which are supposed to be more closer to the application with the pivotal data being in place. But maybe there is a sweet spot between that you have for specific topics, one or two topics to follow up in a more In A quicker fashion, in one or two months' time period. after the PDEV, if something is changed to get back, controlled correspondence is another way, but maybe not the most flexible for a scientific discussion. So maybe there could be opportunities for one or two topics and a meeting, like a type 2A meeting or something, shorter time frame meetings, in between PDEV and the pre-ANDA meeting.

Giuseppe Randazzo, MS: So, a shorter meeting structure. OK, that's a note taking. No, we appreciate that. Trust me. I see someone in the audience is waiting to speak, and there might be some folks online after I have one more audience, sir.

Andrew Cooper, PhD: So, it's Andrew Cooper, you really should know me from this morning. Yeah, so I didn't know who was standing ovations. In this forum, but when I see this slide, that's kind of my personally, that's my feeling as a scientist, because I'm, you know, seeing a kind of opening up of that engine, and I think that sort of me personally looks very exciting. I'm going to throw in a few cautions at this point, because I'm kind of thinking, you know, how this how this will play out in, and and there'll be there will be concerns within the industry about about this, because I mean resource is always one thing, I think #5 is probably the most difficult thing, because if you're talking about practical resource, we usually haven't got enough of that to do all the projects we want to work on. But I think the other thing that will need to be looked at quite carefully, I think as you've recognised, is that it's going to need a kind of a framework, some discipline. Because if you let people like me loose in this, without that, I'll be lost to the company and they won't, that isn't what I'm paid to do. And so I think that, you know, having some framework and some structure within CRCG whereby individuals from individual companies are involved in it have got some idea of what time commitments involved and then get that agreed. That kind of thing is really important within companies, you can't just let people loose to collaborate, unfortunately. I mean, I wish life wasn't like that, but it is, but the one thing I would like to caution against a little bit is that, while I think I agree that the CRCG seems like the way to make this work. Um… Personally, if that, if that kind of come, if that comes at the expense of direct interaction between industry experts and the FDA's own experts, I think we'll lose the power of it. So, the challenge is going to be how you construct a framework that maintains the right degree of… separation between FDA experts and industry experts, but also allows the right degree of interaction that can really get to the best science to deliver the best outcomes for the industry.

Giuseppe Randazzo, MS: So, Sam is ready to chime in, but just to repeat a few words, you talked about framework structure, essentially governance. That's all fair and that's something things we're talking about here and hopefully continue to have the conversation with Sam.

Robert Lionberger, PhD: Yeah, so again, I think you want you, as you, as you know, the comments on the meetings came up, that there's venues for companies to interact directly with FDA in sort of application-specific contexts that we, you know, negotiate through our user fee agreement and, you know, and resource those, you know, appropriately for that. So this is really about things that are not, you know, not, you know, before the individual, this is

my product and I want some feedback on it, right? We have ways for that direct interaction to happen already. This is a, you know, a little bit above that to say, like, can we before, you know, a guidance is posted or what type of, what's the problem, what type of study could handle this, what are the ways that the interactions can happen around that? And, you know, and that's why I think the CRCG aspects can be very valuable. And, you know, Brandon, can, you know, you've been involved with the device aspect, the CRCG has sort of facilitated a group discussion there. You know, and maybe you can give some comments on how that has gone. But I think, but I do agree with your comment on, in order for this to really work, industry has got to sort of send people, you know, at least a few times a year to some working group interaction where they can, you know, express, you know, the feedback and interactions and get the, you know, and get the right people with the technical, with both the technical expertise and the knowledge of, you know, what problem do I have to solve to get this application, you know, submitted.

Giuseppe Randazzo, MS: Thank you, Rob. Sam.

Sam Raney, PhD: Actually, that's a great segue. Thanks, Andrew. I agree with everything you've said, and I think you're right on point. Before unleashing such a seductive idea in a public forum, we have actually been piloting this within the CRCG through expert committees. And one of the things that these expert committees, and I think Jim and Brandon, who actually sits on one of the expert committees, can even speak about this. As we've explored this, a core principle was access, to make sure that there was a completely open access to all companies within the generic drug space that had something to contribute. And as long as they had something to contribute, they were welcomed into the expert committee. And the expert committees were also quite focused. There's a few expert committees, actually, that we have operating at the moment. But one of them, for example, is overseeing a particular GDUFA research priority that was defined a couple of years ago on a particular project. That expert committee helped to design, and this is actually step one there, they actually designed a funding opportunity announcement that was then put out by the CRCG to which proposals were received and that was actually awarded. And after it was awarded, that university reports back to the expert committee on a quarterly basis to describe how the research is going, and the expert committee helps to guide the next steps of that research. And in fact, even moving into step 4 there, members of this expert committee have helped to provide supplies to help keep that research moving forward. And we haven't moved beyond that, but that's one example of an expert committee. Another expert committee is a drug device combination products expert committee that essentially is helping to identify completely alternative approaches to the foundations that FDA has kind of established as the current approach. And I'll let Brandon speak to his experience on that. Maybe I'll let Jim speak a little bit to that as well. But core

to these are just having explored the feasibility for being able to operationalize the ideas here as a complement, not a substitute, a complement to the structural kind of ANDA-specific regulatory meetings on specific products where you can only discuss your product and that specific product. The CRCG is a broader forum meant to kind of be on broader platform issues and an opportunity for industry to collaborate among themselves with FDA, with industry, in kind of a space that's distinct from all the opportunities that the kind of pre-ANDA, regulatory meetings provide. Would you like to kind of comment on your experience with that?

Brandon Wood, MS: Yeah, absolutely. So I am sitting on the Drug Device Combination Product Expert Committee, and I think first, you know, my first takeaway, it's a harmonious collection of industry, academia, and FDA. And I think almost immediately you saw the value of structured collaboration to what Ahmed was talking about. And, you know, just to give a quick anecdote of how this, you know, is visible, you know, almost in that advised category, right? You know, there is understanding, identifying and understanding the issue. And, you know, I kind of laughed a bit because what we were presenting was not too far off than what we had presented back in 2021, I think it was, for the drug device combination product 101. And, you know, there was this kind of realization moment where, again, harmoniously amongst industry, academia, and FDA, it's a real honest discussion. Like, well, why haven't, what's stopping us from from really moving this forward. And I think more importantly, what can we do to take it to that next step? And I think there were some avenues that were identified that are actively being worked on, but just the fact that we've gotten to that step where we've broken out and if we had we've had these honest, you know, discussions and work streams now to work in a direction that will lead to change eventually. I think that already shows you, you know, with that structured collaboration, immediately in a couple of months, we had already exceeded what we've done over the last four or five years. So I just think, you know, again, force multiplier. And I think you made another point, Andy, you know, you know, I think one of the big points in the acknowledgements was that this engine should have the ability to run without industry. And when industry comes in, it again becomes this force multiplier to help the engine, you know, continue and move forward. But, you know, just again, a quick anecdote in terms of my experience, it's been incredibly positive. It's been, you know, honest and open. on a challenge that I think many companies have presented on, have discussed, you know, publicly over the last many years. And I already think we're advancing beyond a point more than we have in the last five years. So it's been a very positive experience. And I would be very excited to put even more structured framework on it. You know, as you see on the slide here, I just think you know, the sky's the limit in terms of these common problems, right? I

think common problems that are priorities, you know, for every company here, I think those are the ones that are really, you know, perfect for this mechanism.

James Polli, PhD: Yeah, I would totally agree about it would be great to have even more structured framework. I think, in many ways, we actually already do. I think the biggest limitation is we're always at the CRCG asking people to do things. You know, just in the last two weeks, I think we've probably asked many people about finalizing things for the fall workshops. There are three of them. I think we probably have a little survey about next year's workshops. I mean, we're always asking people for things. Really, really appreciate everyone's willingness to participate. So, Andrew, your comment about structure, your first comment there really resonated with me. You mentioned #5. Actually, we've actually done that in one case. Xiaoming did a heroic effort of working with particle size, uh... vendors. So it was a kind of a very special group, and I think, in a way, I guess my comment about structure would be, it'd be great if we had like an annual calendar. And I think I've told you before, actually my favorite meeting is actually the AAPS meeting, that's an existing meeting, I think everyone here probably goes to that.

Giuseppe Randazzo, MS: I did not, I did not pay him for that. Good, Jim, continue.

James Polli, PhD: I mean, but we're always asking people for things and people are very gracious. But I think it would be good to have sort of a... Yeah, like an annual calendar of event, an annual event, like yeah.

Giuseppe Randazzo, MS: Thank you very much. And you know, in the interest of time, I know we're out of time, yep, Xiaoming, I do want to give one more comment as well as we wrap up, and I think Rob will wrap up.

Xiaoming Xu, PhD: Yeah, I want to comment on the point #5, which again, collaboration. I know it sounds like we're asking generic industry to work together. Seems like it's, you know, it's a very competitive space and it's a very very thin margin of profit. But I do believe there is a common benefit to the whole industry, because when we are trying to work on the problem individually, we may not realize how common is the problem that we all share, that when we are working together, that reveal, again, our lack of understanding on certain things that allow us to really find ways to work together. And Jim brought up an example, which, again, before we actually were able to do, I was also very comfortable saying that we bring many vendors that are highly competitive in the space of developing instruments out to the industry. How can they work together and running the samples and willing to share experiences, results openly? And it turns out that everyone agree with the problem more clearly or willing to contribute to solving the problem once they understand, OK, this is the... the challenge that facing the industry, facing the FDA, and they're more willing to help

to work together. So I do think it is challenging, but is workable to bring industry partners together. And I think it's really needed. Otherwise, we're trying to individually solving the problem. in one company that, again, become too difficult. And then I agree with Rob. Again, the research we're talking about is more taking longer time. The pre-ANDA those meetings happen usually at the end phase of knowledge already acquired. What we are discussing here require many years of effort working together to overcome to generating the knowledge and to share. I think, again, it's to the benefit of the whole industry, not just the individual company.

Giuseppe Randazzo, MS: That's helpful. Thank you, sir. I'm going to come back to you. I just want to give a couple of panelists an opportunity to speak as well. Any other final thoughts? If not, that's okay. I just want to give you an opportunity. Sir.

Andrew Cooper, PhD: Yes, so thanks for all the comments. They really helped, I think. I just wanted to comment on the collaboration between companies actually, because that there are quite a few forms in which that happens already in terms of industry consortium. So, I think there's no fundamental problem with that. I mean, it often suffers from the same problem, asking people to do things. You know, and so there's always some limit to what can be done, but I think it's generally understood across the industry that there are things we can work on together that are pre-competitive and super-competitive that can actually help to these things.

Giuseppe Randazzo, MS: Thank you very much. We are certainly over time, but I'm going to, is there any comments or any closing statements anyone wants to make? If not, that'll be me.

Tausif Ahmed, PhD: Yeah, I just have just one few, one or two comments if I could make. Yeah, I think the major points are discussed. The major challenge among generic industry is sharing of data. And I think that mindset has to change that once we share the data, it will benefit the.. the entire industry. I think the one approach which or one model which we could think of is where the data generated could be kind of be shared as a part of a consortium that could be utilized to develop some model. I think in past There were some efforts on developing ocular models for extrapolating from preclinical to clinical, but that didn't go that far. One approach on that and the other is many companies, they generate data on complex generics and if there are any physicochemical parameters which are not matching. what impact it has on the in vivo outcome. Some of that data can also be shared and the overall outcome can be conceptualized in form of a guidance or I mean, I don't know how to put in, but I think we've been talking of technical imports, part of expert committees, but the key is that generic companies are sitting on plethora of data. So how

can that data be utilized to solve common problems? I think that is one area which also can be looked into. Just one comment from my end. Thank you.

Giuseppe Randazzo, MS: Thank you, sir.

Anuj Kumar Saini, PhD: So, in addition, yes, I echo Dr. Tausif, but I think you made a very important point: sharing your data through a consortium. It's a mutual, you know, recognition of data with all the industry colleagues as well as regulators. And other important point is, you know, how industry can be engaged in already identified and funded research ongoing activities where there are troubleshooting the ongoing research. In that case, you know how industry can be helpful in accelerating or troubleshooting the research activity which are already identified and ongoing at multiple labs. So that's another point. I mean, very short, I just want to put forward in the framework.

Giuseppe Randazzo, MS: Thank you very much. And before I hand it over to Rob, one shameless plug to feed off of Jim's comment. We were cut short in our conversation here, right? So we went along, I know there's much more to talk about. We will, speaking of the GRX and biosimilars meeting in November AAPS, we are going to work with Sam and the FDA to have this type of conversation in a work group setting where we're going to have FDA, industry and others, collaborators sitting at tables having conversations just similar to this to figure out if that's a vehicle or industry and FDA can collaborate to have further conversations. So that was my one shameless plug and now I'll turn it over to Rob.

Robert Lionberger, PhD: All right, thank you, G. All right, and this is our closing remarks for the meeting. So all of you on the panel here, you have to sit here and listen to the closing remarks. You don't get to escape. You don't get to escape a little bit early. But I really want to thank everyone who participated on the panels and as the speakers. That's the important part of this, to bring that input and that idea. And so, without you doing that, this meeting wouldn't happen, so I want to thank those people.

I want to thank also our session chairs, mainly from FDA, but also from the industry, to, you know, who did the logistic organizing and putting together the panels and, you know, corralling people and their topics and things like that. And, you know, sometimes that's thankless work, but we appreciate all the session chairs that are listed in there.

You know, I also want to recognize our co-chairs for the workshops, both of which are here, Sam and I'm Ahmed, who overall put together the vision for the workshop in a OGD OPQ collaboration. So I recognize you two for that.

And I also recognize behind the scenes, some of the people from, especially from ORS that worked on this, especially Sara Lomonaco, Jessie Floura, who led the organization parts of it, and the many members of the ORS project management and research management

teams who are here, including Christina, Eileen. Sarah Kim, Prachi, Calliope, Karen Bengston, all of you who are back, all the people who are back there and working at the desk there who did all the logistics around these activities to make the workshop flow. Again, and Shivangi, who you probably all know her because every time you logged into the wrong link, she sent you a Teams message telling you what the right link was. I think that's probably the most thankless job here, so we really appreciate her doing that and keeping all the online people in the right place, and so there's a lot of things that made this happen.

So, just to close, a few things that I really learned from here, and that's always… what we want to try from our FDA's perspective, what have we learned here?

Again, about nitrosamines, I think we heard again that this is a huge problem for the generic industry. And if we don't come up with efficient solutions, working both on the reformulation side, like how do you get rid of them, and the sort of acceptable limits, how do we use best available science to catch up in this category, we're going to be in a situation where lots of companies probably are going to make a decision to exit the market rather than maintaining supply of those products. And that's a really critical thing. And it's important for us to, again, rehear that in this context as we think about what we have to do next. But it's still a problem that's remaining. And it's gonna be with us for the next, that's still a consequence that we have to avoid by diligently working on all of those aspects of that product.

Also, yesterday we heard about AI tools, and the thing I took away there is really moving toward the idea of how do you get to reliable AI? And, you know, as to what's the research topic? And it's not just ask the LLM, that's sort of deterministic and that, but combining that, I think we heard from Joga, like, how do you combine that with systems and data sources that are reliable, that you can then get to high reliability things? I think you all want that, because, you know, you know, the reality is FDA is going to have AI tools read your application. And you want them to give the accurate picture of that to our reviewers. Our reviewers are still going to make the decisions, but they're going to be doing things that are assisted by AI tools in the future. And we want those tools to be reliable and, you know, improve the efficiency of our system and get back to you.

But, you know, we also heard today a little bit about interest in, you know, can we be more transparent about people checking their submissions before they sent in, right, is a way that we can think about how that if FDA has ways we look at submissions, you know, that's not a secret. We're not keeping that secret from you. You know, we want to be transparent so you can know what we're going to look for in that, and hopefully that leads to a more efficient future.

You know, in today's workshop, also heard again, always we learn interesting things and see what the perspectives are. Some of the things I heard today were some of the challenges of like, well, you know, it's really important you put out this Q1, Q2 new law that allows us to release that. But the thing really is, well, what if I have a small Q1Q2 difference, right? You tell me there's a difference, right? I really want to know, you know, can I actually, is that difference going to be okay? And I think that's part of the broader question of improving the scientific foundation and what cases are Q and Q2 differences, not important, not critical to successful therapeutic substitution of the product.

And, you know, also heard in that area about, you know, some of the challenges, especially for some of the complex active ingredients, the cost of the RLD, being, you know, being a critical factor, and you know also heard about, you know, how do you use global products that may be available, more affordable, and we sort of believe that they're very similar or the same as the brand product, you know, and that's sort of a change in context. We used to hear people want to use global competitors because there were restricted distribution systems in the US, now it becomes more of an economic. aspect. But there's a scientific aspect of that in terms of the bridging, right? Can I do a small number of experiments that show these products are the same, and then I have a larger amount of material that I can work for, but also be confident that it's also the same? So I think there's a lot of value in thinking through the scientific work that underlies that.

And then again, also in the discussions, we heard about like thinking about as we move into more complex products and in vitro methods, right? For in vivo studies, well, we have 80 to 125 and everybody knows what the limit is, right? But for the in vitro studies, well, what's the appropriate limit and how do you develop them? And behind that, there's a lot of scientific work. And sometimes that involves some of our mechanistic modeling and simulations. They will, look, I can tell you what particle size is going to change the bioavailability. That's an appropriate way to set an in vivo limit. But I think that's something that, as those tools become more and more used, we want to be more and more clear about what's the acceptance criteria, what are some of the tools you can use to justify the size. Now I can measure the particle size. We sort of said, well, if they're the same, we'll approve you. What if they're a little bit different? Right? Now we have to have a discussion. What's the framework for that? And I think that's something that's essential to do, to have efficient approaches to complex generics. As you know, we don't have multiple review cycles. Well, you know, keep measuring this. It's a little bit different. Keep arguing about, is that okay? Is that close enough? Right? What's our framework for doing that? And I think that's an important aspect of the scientific work to really, as we go to the next level of knowledge there, to be more clear on these are the limits that are necessary for the products to be the same, and that will be of an appropriate element of efficiency.

So with that, and then, you know, again, that's just a few of the things that I wrote down, but we also like, well, we recorded this, and so, you know, we'll go back and look at this, and we also will go look back at the docket. and what people, you know, what people said as we reflect on this to try to really capture, you know, what are the things that, you know, maybe we didn't realize, you know, many of the things we do know, but now we hear again that these are becoming more important because the context change. Like every success you have, well, now we have a great framework for Q and Q2 products. I don't want the non-Q and Q2 products, right? Every success opens up a new set of challenges that now become the limiting one. So we constantly doing this every year to look at that and look at the various aspects of that.

So again, thank you all for participating. Thank you for those who joined online. We also expect you who joined online to make comments to the docket. And I think also, like I think we have a survey for them, maybe. Yes, we do have a survey, so we want to hear about your feedback on the workshop as well. To improve that every year, we try to do different things to get different ways that we can engage with you. So with that, thank you all for participating, and have a great afternoon.